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The Western Journal of Medicine

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Warnings: *Angioedema* Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including VASOTEC. In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered.** (See ADVERSE REACTIONS.)

Hypotension Excessive hypotension is rare in uncomplicated hypertensive patients treated with VASOTEC alone. Patients with heart failure given VASOTEC commonly have some reduction in blood pressure, especially with the first dose, but discontinuation of therapy for continuing symptomatic hypotension usually is not necessary when dosing instructions are followed, caution should be observed when initiating therapy. (See DOSAGE AND ADMINISTRATION.) Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure, hyponatremia, high-dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in patients with heart failure), reduce the diuretic dose, or increase salt intake cautiously before initiating therapy with VASOTEC in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See PRECAUTIONS, *Drug Interactions* and ADVERSE REACTIONS.) In patients at risk for excessive hypotension, therapy should be started under very close medical supervision and such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart disease or cardiovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of VASOTEC, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of VASOTEC or concomitant diuretic may be necessary.

Neutropenia/Agranulocytosis Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Precautions: *General: Impaired Renal Function* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or VASOTEC may be required.

Evaluation of patients with hypertension or heart failure should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hyperkalemia Elevated serum potassium (>5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. In clinical trials in heart failure, hyperkalemia was observed in 3.8% of patients, but was not a cause for discontinuation.

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with VASOTEC. (See *Drug Interactions*.)

Surgery/Anesthesia In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients

Angioedema Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension Patients should be cautioned to report lightheadedness, especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions

Hypotension: Patients on Diuretic Therapy Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Agents Causing Renin Release The antihypertensive effect of VASOTEC is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents VASOTEC has been used concomitantly with beta-adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, prazosin, and digoxin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium VASOTEC attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium-sparing agents should generally not be used in patients with heart failure receiving VASOTEC.

Lithium Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant VASOTEC and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium.

Pregnancy—Category C. There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose).

Radioactivity was found to cross the placenta following administration of labeled enalapril to pregnant hamsters.

There are no adequate and well-controlled studies of enalapril in pregnant women. However, data are available that show enalapril crosses the human placenta. Because the risk of fetal toxicity with the use of ACE inhibitors has not been clearly defined, VASOTEC® (Enalapril Maleate, MSD) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Postmarketing experience with all ACE inhibitors thus far suggests the following with regard to pregnancy outcome. Inadvertent exposure limited to the first trimester of pregnancy has not been reported to affect fetal outcome adversely. Fetal exposure during the second and third trimesters of pregnancy has been associated with fetal and neonatal morbidity and mortality.

When ACE inhibitors are used during the later stages of pregnancy, there have been reports of hypotension and decreased renal perfusion in the newborn. Oligohydramnios in the mother has also been reported, presumably representing decreased renal function in the fetus. Infants exposed *in utero* to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion with the administration of fluids and pressors as appropriate. Problems associated with prematurity such as patent ductus arteriosus have occurred in association with maternal use of ACE inhibitors, but it is not clear whether they are related to ACE inhibition, maternal hypertension, or the underlying prematurity.

Nursing Mothers. Milk in lactating rats contains radioactivity following administration of ^{14}C enalapril maleate. It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

Pediatric Use Safety and effectiveness in children have not been established.

Adverse Reactions: VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2987 patients.

HYPERTENSION The most frequent clinical adverse experiences in controlled trials were: headache (5.2%), dizziness (4.3%), and fatigue (3%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.4%), nausea (1.4%), rash (1.4%), cough (1.3%), orthostatic effects (1.2%), and asthenia (1.1%).

HEART FAILURE The most frequent clinical adverse experiences in both controlled and uncontrolled trials were: dizziness (7.9%), hypotension (6.7%), orthostatic effects (2.2%), syncope (2.2%), cough (2.2%), chest pain (2.1%), and diarrhea (2.1%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in both controlled and uncontrolled clinical trials were: fatigue (1.8%), headache (1.8%), abdominal pain (1.6%), asthenia (1.6%), orthostatic hypotension (1.6%), vertigo (1.6%), angina pectoris (1.5%), nausea (1.3%), vomiting (1.3%), bronchitis (1.3%), dyspnea (1.3%), urinary tract infection (1.3%), rash (1.3%), and myocardial infarction (1.2%).

Other serious clinical adverse experiences occurring since the drug was marketed or adverse experiences occurring in 0.5% to 1% of patients with hypertension or heart failure in clinical trials in order of decreasing severity within each category:

Cardiovascular Cardiac arrest, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see WARNINGS, *Hypotension*); cardiac arrest, pulmonary embolism and infarction, rhythm disturbances, atrial fibrillation, palpitation.

Digestive Ileus, pancreatitis, hepatitis or cholestatic jaundice, melena, anorexia, dyspepsia, constipation, glossitis, stomatitis.

Musculoskeletal Muscle cramps.

Nervous/Psychiatric Depression, confusion, ataxia, somnolence, insomnia, nervousness, paresthesia.

Urogenital Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Respiratory Bronchospasm, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection.

Skin Herpes zoster, urticaria, pruritus, alopecia, flushing, hyperhidrosis.

Special Senses Blurred vision, taste alteration, tinnitus.

A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgias/arthritis, myalgias, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash and other dermatologic manifestations.

Angioedema Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients following the initial dose or during extended therapy. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. In heart failure patients, hypotension occurred in 6.7% and syncope occurred in 2.2% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 1.9% of patients with heart failure. (See WARNINGS.)

Clinical Laboratory Test Findings

Serum Electrolytes Hyperkalemia (see PRECAUTIONS), hyponatremia.

Creatinine, Blood Urea Nitrogen In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.) In patients with heart failure who were also receiving diuretics with or without digitalis, increases in blood urea nitrogen or serum creatinine, usually reversible upon discontinuation of VASOTEC and/or other concomitant diuretic therapy, were observed in about 11% of patients. Increases in blood urea nitrogen or creatinine were a cause for discontinuation in 1.2% of patients.

Hemoglobin and Hematocrit Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g% and 1.0 vol%, respectively) occur frequently in either hypertension or heart failure patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown) In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported. A few cases of hemolysis have been reported in patients with G6PD deficiency.

Liver Function Tests Elevations of liver enzymes and/or serum bilirubin have occurred.

Dosage and Administration. *Hypertension* In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with VASOTEC to reduce the likelihood of hypotension. (See WARNINGS.) If the patient's blood pressure is not controlled with VASOTEC alone, diuretic therapy may be resumed.

If the diuretic cannot be discontinued, an initial dose of 2.5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, *Drug Interactions*.)

The recommended initial dose in patients not on diuretics is 5 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 10 to 40 mg per day administered in a single dose or in two divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice-daily administration should be considered. If blood pressure is not controlled with VASOTEC alone, a diuretic may be added.

Concomitant administration of VASOTEC with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium. (see PRECAUTIONS)

Dosage Adjustment in Hypertensive Patients with Renal Impairment The usual dose of enalapril is recommended for patients with a creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≤ 30 mL/min (serum creatinine > 3 mg/dL), the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Heart Failure VASOTEC is indicated as adjunctive therapy with diuretics and digitalis. The recommended starting dose is 2.5 mg once or twice daily. After the initial dose of VASOTEC, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, *Drug Interactions*.) If possible, the dose of the diuretic should be reduced, which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of VASOTEC does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension. The usual therapeutic dosing range for the treatment of heart failure is 5 to 20 mg daily given in two divided doses. The maximum daily dose is 40 mg. Once-daily dosing has been effective in a controlled study, but nearly all patients in this study were given 40 mg, the maximum recommended daily dose, and there has been much more experience with twice-daily dosing. In addition, in a placebo-controlled study which demonstrated reduced mortality in patients with severe heart failure (NYHA Class IV), patients were treated with 2.5 to 40 mg per day of VASOTEC, almost always administered in two divided doses. (See CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects*.) Dosage may be adjusted depending upon clinical or hemodynamic response. (See WARNINGS.)

Dosage Adjustment in Patients with Heart Failure and Renal Impairment or Hyponatremia In patients with heart failure who have hyponatremia (serum sodium < 130 mEq/L) or with serum creatinine >1.6 mg/dL, therapy should be initiated at 2.5 mg daily under close medical supervision. (See DOSAGE AND ADMINISTRATION, *Heart Failure*, WARNINGS, and PRECAUTIONS, *Drug Interactions*.) The dose may be increased to 2.5 mg b.i.d., then 5 mg b.i.d. and higher as needed, usually at intervals of four days or more, if at the time of dosage adjustment there is not excessive hypotension or significant deterioration of renal function. The maximum daily dose is 40 mg.

For more detailed information, consult your MSD Representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486 J9VS54R(818)

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MACGREGOR, ROBERT J., Sierra Vista. Died Jun 30, 1989, aged 64. Graduate of University of California, San Francisco, School of Medicine, 1955. Licensed in Arizona in 1968. Dr MacGregor was a member of the Cochise County Medical Society.

California Medical Association

BURRE, SAMUEL PINK, Eureka. Died Oct 24, 1989, aged 89. Graduate of Loyola University School of Medicine, Chicago, 1929. Licensed in California in 1930. Dr Burre was a member of the Humboldt-Del Norte Medical Society.

FESSLER, FRANCIS W., Reedley. Died Oct 27, 1989, aged 75. Graduate of University of Wisconsin, Madison, 1950. Licensed in California in 1956. Dr Fessler was a member of the Fresno-Madera Medical Society.

HALLEY, EDMUND P., Stockton. Died Sep 29, 1989, aged 89. Graduate of Northwestern University Medical School, Chicago, 1924. Licensed in California in 1939. Dr Halley was a member of the San Joaquin County Medical Society.

LAMBERT, RICHARD H., Santa Barbara. Died Sep 27, 1989, aged 76. Graduate of University of Iowa, Iowa City, 1936. Licensed in California in 1946. Dr Lambert was a member of the Santa Barbara County Medical Society.

ORWIG, JAMES B. III, San Diego. Died Sep 16, 1989, aged 54. Graduate of University of Michigan, Ann Arbor, 1962. Licensed in California in 1968. Dr Orwig was a member of the San Diego County Medical Society.

REY, GEORGE E., Porterville. Died Aug 12, 1989, aged 79. Graduate of Wayne State University, Detroit, 1940. Dr Rey was a member of the Tulare County Medical Society.

SHON, CHARLES M., Los Gatos. Died Oct 4, 1989, aged 57. Graduate of Marquette, 1956. Licensed in California in 1960. Dr Shon was a member of the Santa Clara County Medical Association.

SOMERS, RAYMOND H., San Jose. Died Sep 30, 1989, aged 92. Graduate of Northwestern University Medical School, Chicago, 1922. Dr Somers was a member of the Santa Clara County Medical Association.

STANTON, JAMES T., Bakersfield. Died Nov 1, 1989, aged 84. Graduate of University of Iowa, Iowa City, 1930. Licensed in California in 1938. Dr Stanton was a member of the Kern County Medical Society.

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Denver Medical Society

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VERPLOEG, RALPH H. Died Oct 31, 1989, aged 90. Graduate of University of Iowa School of Medicine, Iowa City, 1927. Licensed in Colorado in 1929.

New Mexico Medical Society

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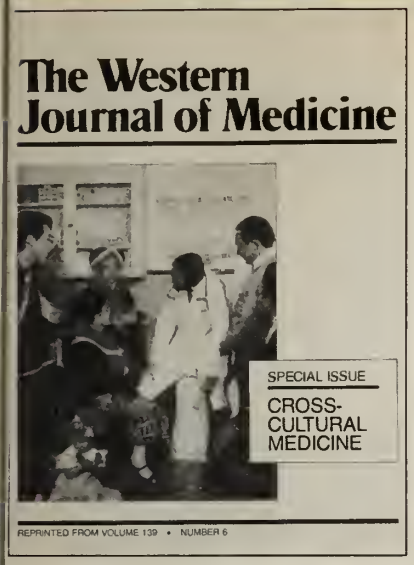

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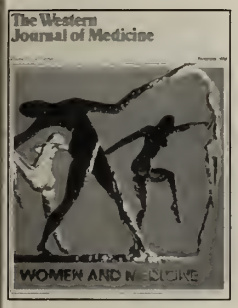

This special issue explores both the professional side of women in medicine and the diagnosis and treatment of women patients. Topics covered include liver disease, women and AIDS, heart disease, hysterectomy, PMS, ovarian cancer, and women physicians and organized medicine. Linda Hawes Clever, MD, Special Issue Editor, 1988.

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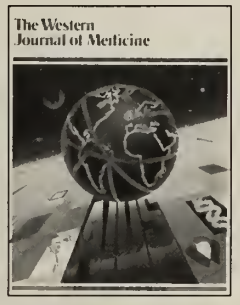

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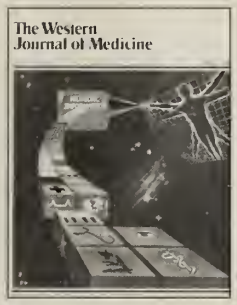

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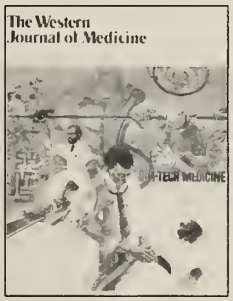

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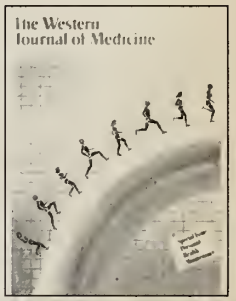

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What's a common denominator of most heart attack victims?

HDL

<35

mg/dL

Mixed hyperlipidemias—elevated cholesterol *and* triglycerides—are common among heart attack victims,[1] and nearly two-thirds of people who developed myocardial infarction in the PROCAM Trial had a low (<35 mg/dL) baseline level of HDL cholesterol.[2]

HEART ATTACK PATIENTS
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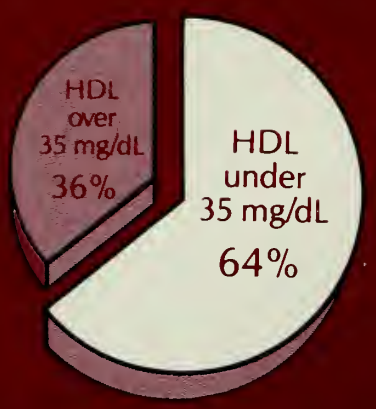

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LOPID is indicated for reducing the risk of coronary heart disease (CHD) in Type IIb patients with low HDL, in addition to elevated LDL and triglycerides, and who have had an inadequate response to weight loss, diet, exercise, and other pharmacologic agents such as bile acid sequestrants and nicotinic acid.

*Defined as a combination of definite coronary death and/or definite myocardial infarction.

References: 1. Goldstein JL, Hazzard WR, Schrott HG, Bierman EL, Motulsky AG. Hyperlipidemia in coronary heart disease. I. Lipid levels in 500 survivors of myocardial infarction. *J Clin Invest.* 1973;52:1533-1543. **2.** Assmann G, Schulte H. *PROCAM-Trial: Prospective Cardiovascular Münster Trial.* Zürich: Panscientia Verlag; 1986:8-9. **3.** Data on file, Medical Affairs Dept, Parke-Davis **4.** Tikkanen MJ, Helve E, Jäättelä A, et al. Comparison between lovastatin and gemfibrozil in the treatment of primary hypercholesterolemia: the Finnish Multicenter Study. *Am J Cardiol.* 1988;62:35J-43J.

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Before prescribing, please see full prescribing information.
A Brief Summary follows.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease (See WARNINGS).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

During the Helsinki Heart Study and in the 1½ year follow-up period since the trial was completed, mortality from any cause was 59 (2.9%) in the Lopid group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the Lopid group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statistically-significantly different from the 29% excess mortality seen in the clofibrate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58% greater trend in the Lopid group (43 vs 27 patients in the placebo group, p=0.056).

In the Helsinki Heart Study, the incidence of total malignancies discovered during the trial and in the 1½ years since the trial was completed was 39 in the Lopid group and 29 in the placebo group (difference not statistically significant). This includes 5 basal cell carcinomas in the Lopid group and none in the placebo group (p=0.06; historical data predicted an expected 4.7 cases in the placebo group). GI malignancies and deaths from malignancies were not statistically different between Lopid and placebo subgroups. Follow-up of the Helsinki Heart Study participants will provide further information on cause-specific mortality and cancer morbidity.

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants – Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts – Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS. 1. **Initial Therapy** – Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy** – Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions** – (A) **Lovastatin:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility** – Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p=0.1). In high dose female rats, there was a significant increase in the combined incidence of benign, and malignant liver neoplasms. In male and female mice, there were no statistically significant differences

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from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately three or ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category B** – Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to Lopid. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lopid is tumorigenic in male and female rats, the use of Lopid in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers** – Because of the potential for tumorigenicity shown for gemfibrozil in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes** – Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. **Liver Function** – Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Use in Children** – Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In the double-blind controlled phase of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group (placebo incidence in parentheses): gastrointestinal reactions, 34.2% (23.8%), dyspepsia, 19.6% (11.9%); abdominal pain, 9.8% (5.6%); acute appendicitis (histologically confirmed in most cases where data are available), 1.2% (0.6%); atrial fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant difference between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5%); fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%).

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study.

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of **musculoskeletal symptoms** (See WARNINGS), and to **abnormal liver function tests** and **hematologic changes** (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patients.

Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *Integumentary:* alopecia.

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

MANAGEMENT OF OVERDOSE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

References: 1. Frick MH, Elo O, Haapa K, et al: Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med* 1987;317:1237-1245. 2. Manninen V, Elo O, Frick MH, et al. Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA* 1988; 260:641-651. 3. Nikkila EA: Familial lipoprotein lipase deficiency and related disorders of chylomicron metabolism. In Stanbury J. B. et al. (eds.): *The Metabolic Basis of Inherited Disease*, 5th ed., McGraw-Hill, 1983, Chap. 30, pp. 622-642

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INFORMATION FOR AUTHORS

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4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs, or Books With No Given Author

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Brief Summary

INDICATIONS AND USAGE: Zovirax Capsules are indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes in certain patients

The severity of disease is variable depending upon the immune status of the patient, the frequency and duration of episodes, and the degree of cutaneous or systemic involvement. These factors should determine patient management, which may include symptomatic support and counseling only, or the institution of specific therapy. The physical, emotional and psycho-social difficulties posed by herpes infections as well as the degree of debilitation, particularly in immunocompromised patients, are unique for each patient, and the physician should determine therapeutic alternatives based on his or her understanding of the individual patient's needs. Thus Zovirax Capsules are not appropriate in treating all genital herpes infections. The following guidelines may be useful in weighing the benefit/risk consideration in specific disease categories.

First Episodes (primary and nonprimary infections—commonly known as initial genital herpes):

Double-blind, placebo-controlled studies have demonstrated that orally administered Zovirax significantly reduced the duration of acute infection (detection of virus in lesions by tissue culture) and lesion healing. The duration of pain and new lesion formation was decreased in some patient groups. The promptness of initiation of therapy and/or the patient's prior exposure to Herpes simplex virus may influence the degree of benefit from therapy. Patients with mild disease may derive less benefit than those with more severe episodes. In patients with extremely severe episodes, in which prostration, central nervous system involvement, urinary retention or inability to take oral medication require hospitalization and more aggressive management, therapy may be best initiated with intravenous Zovirax.

Recurrent Episodes:

Double-blind, placebo-controlled studies in patients with frequent recurrences (6 or more episodes per year) have shown that Zovirax Capsules given for 4 to 6 months prevented or reduced the frequency and/or severity of recurrences in greater than 95% of patients. Clinical recurrences were prevented in 40 to 75% of patients. Some patients experienced increased severity of the first episode following cessation of therapy; the severity of subsequent episodes and the effect on the natural history of the disease are still under study.

The safety and efficacy of orally administered acyclovir in the suppression of frequent episodes of genital herpes have been established only for up to 6 months. Chronic suppressive therapy is most appropriate when, in the judgement of the physician, the benefits of such a regimen outweigh known or potential adverse effects. In general, Zovirax Capsules should not be used for the suppression of recurrent disease in mildly affected patients. Unanswered questions concerning the human relevance of *in vitro* mutagenicity studies and reproductive toxicity studies in animals given very high doses of acyclovir for short periods (see Carcinogenesis, Mutagenesis, Impairment of Fertility) should be borne in mind when designing long-term management for individual patients. Discussion of these issues with patients will provide them the opportunity to weigh the potential for toxicity against the severity of their disease. Thus, this regimen should be considered only for appropriate patients and only for six months until the results of ongoing studies allow a more precise evaluation of the benefit/risk assessment of prolonged therapy.

Limited studies have shown that there are certain patients for whom intermittent short-term treatment of recurrent episodes is effective. This approach may be more appropriate than a suppressive regimen in patients with infrequent recurrences.

Immunocompromised patients with recurrent herpes infections can be treated with either intermittent or chronic suppressive therapy. Clinically significant resistance, although rare, is more likely to be seen with prolonged or repeated therapy in severely immunocompromised patients with active lesions.

CONTRAINDICATIONS: Zovirax Capsules are contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulation.

WARNINGS: Zovirax Capsules are intended for oral ingestion only.

PRECAUTIONS: General: Zovirax has caused decreased spermatogenesis at high doses in some animals and mutagenesis in some acute studies at high concentrations of drug (see PRECAUTIONS—Carcinogenesis, Mutagenesis, Impairment of Fertility). The recommended dosage and length of treatment should not be exceeded (see DOSAGE AND ADMINISTRATION).

Exposure of Herpes simplex isolates to acyclovir *in vitro* can lead to the emergence of less sensitive viruses. The possibility of the appearance of less sensitive viruses in man must be borne in mind when treating patients. The relationship between the *in vitro* sensitivity of Herpes simplex virus to acyclovir and clinical response to therapy has yet to be established (see CLINICAL PHARMACOLOGY—Microbiology).

Because of the possibility that less sensitive virus may be selected in patients who are receiving acyclovir, all patients should be advised to take particular care to avoid potential transmission of virus if active lesions are present while they are on therapy. In severely immunocompromised patients, the physician should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses which may not fully respond to continued acyclovir therapy.

Drug Interactions: Co-administration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of 50, 150 and 450 mg/kg given by gavage. There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors. In 2 *in vitro* cell transformation assays, used to provide preliminary assessment of potential oncogenicity in advance of these more definitive life-time bioassays in rodents, conflicting results were obtained. Acyclovir was positive at the highest dose used in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice. Acyclovir was negative in another transformation system considered less sensitive.

In acute studies, there was an increase, not statistically significant, in the incidence of chromosomal damage at maximum tolerated parenteral doses of 100 mg/kg acyclovir in rats but not Chinese hamsters; higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters. In addition, no activity was found after 5 days dosing in a dominant lethal study in mice. In 6 of 11 microbial and mammalian cell assays, no evidence of mutagenicity was observed. At 3 loci in a Chinese hamster ovary cell line, the results were inconclusive. In 2 mammalian cell assays (human lymphocytes and L5178Y mouse lymphoma cells *in vitro*), positive responses for mutagenicity and chromosomal damage occurred, but only at concentrations at least 400 times the acyclovir plasma levels achieved in man.

Acyclovir has not been shown to impair fertility or reproduction in mice (450 mg/kg/day, p.o.) or in rats (25 mg/kg/day, s.c.). At 50 mg/kg/day s.c. in the rat, there was a statistically significant increase in post-implantation loss, but no concomitant decrease in litter size. In female rabbits treated subcutaneously with acyclovir subsequent to mating, there was a statistically significant decrease in implantation efficacy but no concomitant decrease in litter size at a dose of 50 mg/kg/day. No effect upon implantation efficiency was observed when the same dose was administered intravenously. In a rat peri- and postnatal study at 50 mg/kg/day s.c., there was a statistically significant decrease in the group mean numbers of corpora lutea, total implantation sites and live fetuses in the F_1 generation. Although not statistically significant, there was also a dose related decrease in group mean numbers of live fetuses and implantation sites at 12.5 mg/kg/day and 25 mg/kg/day, s.c. The intravenous administration of 100 mg/kg/day, a dose known to cause obstructive nephropathy in rabbits, caused a significant increase in fetal resorptions and a corresponding decrease in litter size. However, at a maximum tolerated intravenous dose of 50 mg/kg/day in rabbits, there were no drug-related reproductive effects.

Intraperitoneal doses of 320 or 80 mg/kg/day acyclovir given to rats for 1 and 6 months, respectively, caused testicular atrophy. Testicular atrophy was persistent through the 4-week postdose recovery phase after 320 mg/kg/day; some evidence of recovery of sperm production was evident 30 days postdose. Intravenous doses of 100 and 200 mg/kg/day acyclovir given to dogs for 31 days caused aspermatogenesis. Testicles were normal in dogs given 50 mg/kg/day i.v. for one month.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p.o.), rabbit (50 mg/kg/day, s.c. and i.v.) or in standard tests in the rat (50 mg/kg/day, s.c.). In a non-standard test in rats, fetal abnormalities, such as head and tail anomalies, were observed following subcutaneous administration of acyclovir at very high doses associated with toxicity to the maternal rat. The clinical relevance of these findings is uncertain. There are no adequate and well-controlled studies in pregnant women. Acyclovir should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Although acyclovir was not teratogenic in standard animal studies, the drug's potential for causing chromosome breaks at high concentration should be taken into consideration in making this determination.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Zovirax is administered to a nursing woman. In nursing mothers, consideration should be given to not using acyclovir treatment or discontinuing breastfeeding.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS—Short-Term Administration: The most frequent adverse reactions reported during clinical trials of treatment with Zovirax Capsules were nausea and/or vomiting in 8 of 298 patient treatments (2.7%) and headache in 2 of 298 (0.6%). Less frequent adverse reactions, each of which occurred in 1 of 298 patient treatments with Zovirax Capsules (0.3%), included diarrhea, dizziness, anorexia, fatigue, edema, skin rash, leg pain, inguinal adenopathy, medication taste and sore throat.

Long-Term Administration: The most frequent adverse reactions reported in studies of daily therapy for 3 to 6 months were headache in 33 of 251 patients (13.1%), diarrhea in 22 of 251 (8.8%), nausea and/or vomiting in 20 of 251 (8.0%), vertigo in 9 of 251 (3.6%), and arthralgia in 9 of 251 (3.6%). Less frequent adverse reactions, each of which occurred in less than 3% of the 251 patients (see number of patients in parentheses), included skin rash (7), insomnia (4), fatigue (7), fever (4), palpitations (1), sore throat (2), superficial thrombophlebitis (1), muscle cramps (2), pars planitis (1), menstrual abnormality (4), acne (3), lymphadenopathy (2), irritability (1), accelerated hair loss (1), and depression (1).

DOSAGE AND ADMINISTRATION: Treatment of initial genital herpes: One 200 mg capsule every 4 hours, while awake, for a total of 5 capsules daily for 10 days (total 50 capsules).

Chronic suppressive therapy for recurrent disease: One 200 mg capsule 3 times daily for up to 6 months. Some patients may require more drug, up to one 200 mg capsule 5 times daily for up to 6 months.

Intermittent Therapy: One 200 mg capsule every 4 hours, while awake, for a total of 5 capsules daily for 5 days (total 25 capsules). Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence.

Patients With Acute or Chronic Renal Impairment: One 200 mg capsule every 12 hours is recommended for patients with creatinine clearance ≤10 ml/min/1.73 m^2

HOW SUPPLIED: Zovirax Capsules (blue, opaque) containing 200 mg acyclovir and printed with "Wellcome ZOVIRAX 200"—Bottles of 100 (NDC-0081-0991-55), and unit dose pack of 100 (NDC-0081-0991-56).

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U.S. Patent No. 4199574

*In controlled studies, recurrences were totally prevented for 4 to 6 months in up to 75% of patients.

IMPROVING LIVES THROUGH ANTIVIRAL RESEARCH

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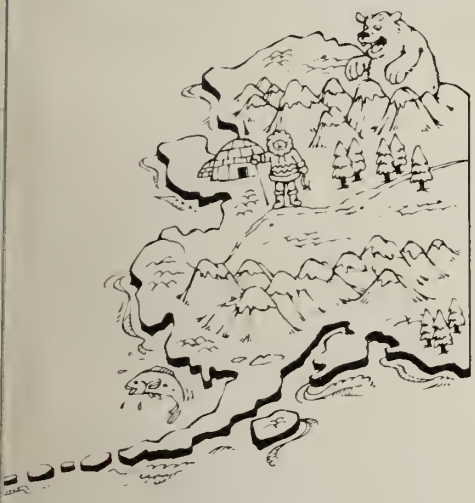

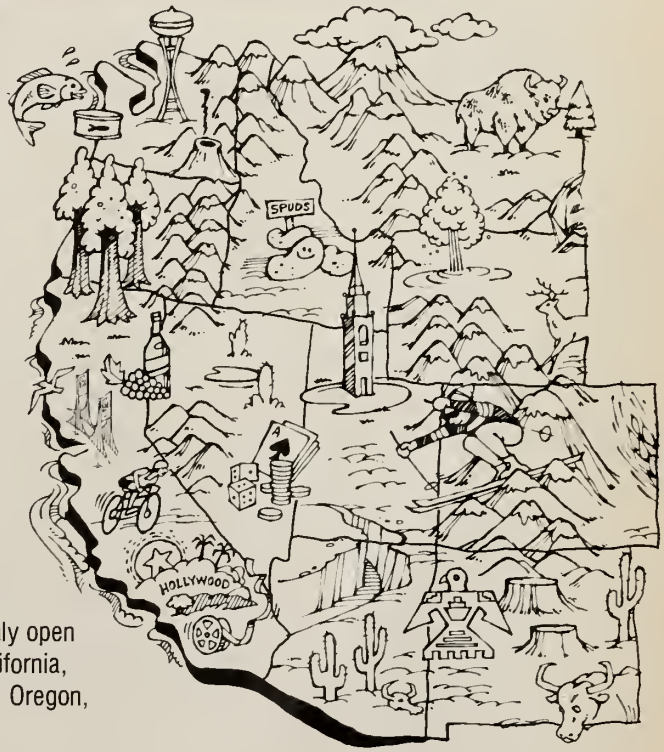

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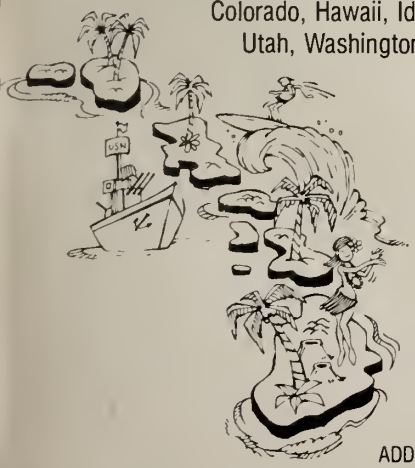

■ **WJM** is clinically oriented, national in scope, and not confined to any single specialty. Your article must be written in **WJM** style and be of interest to our readers. If, in the judgment of the editorial board, no articles meet the standards of **WJM,** no award will be made.

ADDITIONAL RULES:

- Articles must be 3,000 to 4,000 words in length. The manuscript must be identified as submitted for consideration for this award.
- Co-authorship is permitted if all authors meet the qualifications. The $1,000 award will be divided equally among the co-authors.
- Articles must conform to **WJM's** style—our style guide, "Information for Authors," appears in the January and July issues, or you may write our editorial department for a copy of the guide.
- Articles will be judged by the editors and the editorial and advisory boards of the journal.
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Continuing Medical Education

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

January 11-12—**Twenty-First Annual Tucson Seminar in Obstetrics and Gynecology.** Arizona Health Sciences Center, DuVal (Main) Auditorium, Tucson. Thurs-Fri. Contact: Lewis Shenker, MD, (602) 626-4555.

January 20—**Current Medical and Surgical Approaches to Urolithiasis.** Mayo Clinic-Scottsdale. Sat. Contact: Mayo Clinic-Scottsdale.

January 25-30—**International Health: Clinical and Community Care.** University of Arizona College of Medicine, Tucson. Thurs-Tues. Contact: (602) 626-7962.

February 9-10—**Series II—Arrhythmias: Interpretation, Diagnosis, and Management.** Medical Education Resources at La Posada Resort, Scottsdale. Fri-Sat. Contact: Deborah Helton, 1 (800) 421-3756.

February 11-16—**International Congress III: Lasers, Stents, and Interventions in Vascular Disease.** Arizona Heart Institute, Scottsdale. Sun-Fri. Contact: Erika Scott, (602) 266-2200.

February 15-17—**16th Annual Frontiers in Ophthalmology.** St Luke's Medical Center and Prentice Eye Institute at Red Lion's La Posada Resort, Scottsdale. Thurs-Sat. Contact: Christine Campbell, (602) 820-7027.

February 15-17—**Emergency Care Update.** Arizona Health Sciences Center, Tucson. Thurs-Sat. Contact: (602) 626-7832.

February 16-17—**Geriatrics in a Changing Society: Enhancing Function—2nd Annual Regional, Multidisciplinary Conference.** Samaritan Institute of Gerontology, Phoenix. Fri-Sat. Contact: Jean Kiernat, (602) 239-5884.

February 22-24—**Geriatric Medicine Update and Board Certification Review Conference.** Doubletree Hotel, Tucson. Thurs-Sat. Contact: Gail Kershner Riggs, (602) 626-6854.

February 23-24—**Mayo Clinic Update on Plastic and Reconstructive Surgery.** Marriott's Mountain Shadows Resort, Scottsdale. Fri-Sat. Contact: Mayo Clinic-Scottsdale.

February 23-25—**Anesthesia for the 1990s.** Arizona Society of Anesthesiologists, Wyndham Paradise Valley Resort, Scottsdale. Fri-Sun. Contact: Beverly Reichter, (602) 246-8901.

February 24—**Diabetes 1990: A Practical Approach to Management IV.** Good Samaritan Regional Medical Center, Phoenix Children's Hospital, and American Diabetes Association at Wyndham Paradise Valley Resort. Sat. Contact: Teri Quesnell, (602) 239-5994.

February 26-March 1—**Practical Radiology—6th Annual Course.** Lowe's Ventana Canyon Resort, Tucson. Mon-Thurs. Contact: (602) 626-7832.

February 27-March 2—**Pediatric Update.** Phoenix Children's Hospital. Tues-Fri. Contact: Susan Fraley, (602) 239-5783.

March 1-2—**Southern Arizona Trauma Conference.** Doubletree Hotel, Tucson. Thurs-Fri. Contact: Lorraine Haertel, PhD, (602) 626-6233.

March 1-3—**Rheumatology for the 90s: A Look Into the Future.** Westin La Paloma Resort, Tucson. Thurs-Sat. Contact: CME, Arizona Health Sciences Center, (602) 626-7832.

March 1-4—**A Continuance of Excellence.** Arizona Academy of Family Physicians, The Registry Resort, Scottsdale. Thurs-Sun. Contact: Nancy Reeves, (602) 249-2021.

March 3-7—**Fourth Annual Magnetic Resonance Imaging Conference.** Barrow Neurological Institute of St Joseph's Hospital and Medical Center at Marriott's Camelback Inn Resort, Scottsdale. Sat-Wed. Contact: Kevin King, RT, (602) 285-3956.

March 8-10—**Recent Advances in Neurology and Neurosurgery—17th Annual Symposium.** Barrow Neurological Institute at Camelback Inn Resort, Scottsdale. Thurs-Sat. Contact: Toby Jardine, (602) 285-3178.

March 14—**Dean's Education Rounds.** Arizona Health Sciences Center, Tucson. Wed. Contact: Jack Roberts, (602) 626-4555.

March 23-24—**Ophthalmic Reviews.** Mayo Clinic-Scottsdale at Scottsdale Sheraton Resort. Fri-Sat. Contact: Mayo Clinic-Scottsdale.

March 27-30—**15th Annual Primary Care Update.** Arizona Health Sciences Center, Tucson. Tues-Fri. Contact: Lynne Mascarella, (602) 626-7832.

March 29-30—**Clinical Reviews.** Mayo Clinic-Scottsdale at The Registry Resort, Scottsdale. Thurs-Fri. Contact: Mayo Clinic-Scottsdale.

March 31—**Nutrition Update for Primary Care Providers.** Arizona Health Sciences Center, Tucson. Sat. Contact: Lynne Mascarella, (602) 626-7832.

April 9-14—**Primary Care Update.** Tucson. Mon-Sat. Contact: Cristy Snow, (602) 626-7946.

April 20-21—**Series I—Coronary Heart Disease Update.** Medical Education Resources at La Posada Resort, Scottsdale. Fri-Sat. Contact: Deborah Helton, 1 (800) 421-3756.

June 22-24—**Thirteenth Annual Pediatrics in the Red Rocks.** American Academy of Pediatrics—Arizona Chapter at Los Abrigados, Sedona. Fri-Sun. Contact: Melanye Wrighton, (602) 230-1949.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Jodi Lee Smith, Postgraduate Courses, Mayo Clinic Scottsdale, (602) 391-8300.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

January 14-19—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Sheraton Kauai Hotel, Poipu Beach, Kauai, Hawaii. Sun-Fri. 21 hrs. $325. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

(Continued on Page 22)

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(Continued from Page 20)

January 26-28—**28th Clinical Conference in Pediatric Anesthesiology.** Children's Hospital of Los Angeles at Los Angeles Airport Marriott Hotel. Fri-Sun. 15 hrs. $250. Contact: Katherine Barky, MD, Pediatric Anesthesiology Conference, Children's Hospital, PO Box 54700, Los Angeles 90054.

February 4-10—**Clinical Update in Anesthesiology.** Biennial Western Conference on Anesthesiology at Stouffer's Wailea Beach Resort, Maui, Hawaii. Sun-Sat. Contact: Murray G. Atnikov, MD, PO Box F110-63, Blaine, WA 98230. (604) 874-5291.

March 5-8—**18th Obstetric Anesthesia Conference.** Ohio State University Hospitals Department of Anesthesiology at Westin, Maui, Hawaii. Mon-Thurs. Contact: Arlene Rogers, 410 West 10th Ave, Columbus, OH 43210. (614) 293-8487.

March 9-13—**64th Congress of the International Anesthesia Research Society.** International Anesthesia Research Society at Sheraton Waikiki Hotel, Honolulu, Hawaii. Fri-Tues. Contact: IARS, 3645 Warrensville Center Rd, Cleveland, OH 44122-5280. (216) 295-1124.

March 17-18—**35th Postgraduate Assembly of Los Angeles County Society of Anesthesiologists.** Los Angeles County Society of Anesthesiologists at Sheraton Universal Hotel, Universal City. Sat-Sun. Contact: LACSA, PO Box 3465, Los Angeles 90051-1465. (213) 483-1581, ext 320.

March 24-25—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Newport Beach Marriott Hotel. Sat-Sun. 9 hrs. $125. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

May 17-20—**California Society of Anesthesiologists 1990 Annual Meeting.** California Society of Anesthesiologists at San Francisco Marriott. Thurs-Sun. 18 hrs. $175. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

May 29-June 3—**UCSD Anesthesiology Review Course.** UCSD at San Diego Princess, San Diego. Tues-Sun. Contact: UCSD.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Avenue, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7186.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

CARDIOLOGY

January 19-20—**Coronary Heart Disease Update.** Medical Education Resources at Desert Inn Hotel, Las Vegas, Nevada. Fri-Sat. Contact: Deborah Wilderson, MER, (800) 421-3756.

January 25-27—**Cardiology '90.** Scripps Memorial Hospital at La Jolla Marriott Hotel. Thurs-Sat. 16 hrs. $325. Contact: Nancy Donegan, 7777 Alvarado Rd, Ste 110, La Mesa 92041. (619) 462-6800.

February 21—**30th Annual Cardiovascular Symposium.** Enloe Hospital and Chico Community Hospital at Esplanade Building, Chico. Wed. 6 hrs. Contact: Linda Morgado, (916) 891-7300, ext 7375.

February 23-25—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Marquis Hotel, Palm Springs. Fri-Sun. Contact: Deborah Wilderson, MER, (800) 421-3756.

March 30-31—**Cardiology for the Clinician.** UCI at Long Beach. Fri-Sat. Contact: UCI.

April 2-11—**Cardiology for the Consultant: A Physicians' Retreat.** Scripps Clinic and Research Foundation at Rancho Santa Fe. 1½ weeks. 40 hrs. $900. Contact: Mary Ann Morris, 860 SW Scherer Rd, Lee's Summit, MO 64063. (816) 524-5780.

April 28—**Current Concepts in Heart Disease.** Grossmont Hospital at Bahia Hotel, San Diego. Sat. 6 hrs. $100. Contact: Continuing Medical Education, Grossmont Hospital, PO Box 158, La Mesa 92044. (619) 589-4153.

May 4-5—**Series II—Arrhythmias: Interpretation, Diagnosis, and Management.** Medical Education Resources at Marriott Hotel, San Diego. Fri-Sat. Contact: MER, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4528. (303) 798-9682.

June 15-16—**Series IV—Cardiac Wellness and Rehabilitation.** Medical Education Resources at Hyatt Union Square, San Francisco. Fri-Sat. Contact: MER, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4528. (303) 798-9682.

June 22-23—**Series I—Coronary Heart Disease Update.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sat. Contact: MER, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4528. (303) 798-9682.

DERMATOLOGY

January 18-20—**Workshop in Dermatopathology.** Scripps Clinic and Research Foundation at Sheraton Grande at Torrey Pines, La Jolla. Thurs-Sat. $400. Contact: Bonny A. Mower, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

January 19-21—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** UCSD at San Diego Princess. Fri-Sun. 20 hrs. Contact: UCSD.

February 21-25—**Problems of the Aging Skin.** Stanford University at Las Vegas, Nevada. Wed-Sun. Contact: Paul Jacobs, Professor of Dermatology, Room R-144, Stanford 94305. (415) 723-7854.

June 8-9—**Southwestern Regional Cutaneous Flap Workshop.** UCLA. Fri-Sat. 15 hrs. Contact: Daniel E. Gormley, 412 W Carroll, Ste 207, Glendora 91740. (818) 963-7684.

EMERGENCY MEDICINE

January 15-19—**Emergency Medicine Symposium I.** UCSD at San Diego Hilton Beach & Tennis Resort. Mon-Fri. 32 hrs. Contact: UCSD.

January 17-21—**9th Annual Emergency Medicine and Acute Care: A Critical Appraisal Series 3.** Emergency Medical Abstracts at Maui, Hawaii. Wed-Sun. 20 hrs. Contact: Bob Cowsill, 6917 Royer Ave, West Hills 91307. (818) 884-8844.

February 17-20—**9th Annual Emergency Medicine and Acute Care: A Critical Appraisal Series 3.** Emergency Medical Abstracts at Las Vegas, Nevada. Sat-Tues. 20 hrs. Contact: Bob Cowsill, 6917 Royer Ave, West Hills 91307. (818) 884-8844.

February 18-21—**9th Annual Emergency Medicine and Acute Care: A Critical Appraisal Series 3.** Emergency Medical Abstracts at Los Angeles. Sun-Wed. 20 hrs. Contact: Bob Cowsill, 6917 Royer Ave, West Hills 91307. (818) 884-8844.

(Continued on Page 26)

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Investigators' evaluations confirm hair growth in male pattern baldness of the vertex

ROGAINE® Topical Solution (minoxidil 2%) is the *first* prescription medication proved effective for male pattern baldness of the vertex. The effect on frontal baldness has not been adequately studied.

Evidence of growth was demonstrated by physician evaluations of 1,431 patients in 27 centers across the United States. Patients were placed on ROGAINE or placebo and evaluated each month for four months. Response was judged to be no growth, new vellus (baby) hair, or minimal, moderate, or dense growth.

In addition, after the placebo group was discontinued, continuous application of ROGAINE over an additional eight months was evaluated to determine if nonvellus growth could be sustained.

START OF STUDY

START OF STUDY

START OF STUDY

Examples of minimal, moderate, and dense growth as evaluated by investigators

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MINIMAL GROWTH

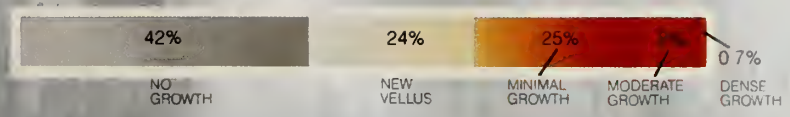
MODERATE GROWTH

DENSE GROWTH

Four-Month Phase

At the end of four months, 34% of 714 patients treated with ROGAINE were evaluated as showing minimal, moderate, or dense growth, while 20% of 717 patients showed minimal, moderate, or dense growth with placebo, a highly significant difference ($P<.0005$).

Rogaine (714)



Placebo (717)

Non-Placebo-Controlled Continuation Phase

After 12 months, dense growth was observed in 8% of the 619 patients treated with ROGAINE, moderate growth in 31%, and minimal growth in 37%. Approximately one fourth of patients showed only vellus hair growth or no growth.

Rogaine (619)

Compliance is Essential

The multicenter studies indicate that a period of *four months or longer* of daily b.i.d. applications of ROGAINE is usually necessary before evidence of hair growth is apparent. Hair growth continued to increase in study subjects over months 5 through 12.

Continuous use is necessary to maintain hair growth. Newly grown hair returns to the untreated state three to four months after cessation of therapy with ROGAINE.

Please see last page for brief summary of prescribing information.

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INDICATIONS AND USAGE
Male pattern baldness (alopecia androgenetica) of the vertex of the scalp. No effect has been seen on frontal baldness. At least four months of treatment are generally required before evidence of hair growth can be expected; further growth continues through one year. The new growth is not permanent, cessation of treatment will lead to its loss in a few months.

CONTRAINDICATIONS
Hypersensitivity to minoxidil, propylene glycol or ethanol

WARNINGS
1. Need for normal scalp: Before starting treatment, make sure that the patient has a normal, healthy scalp. Local abrasion or dermatitis may increase absorption and hence the risk of side effects.
2. Potential adverse effects: Although extensive use of topical minoxidil has not revealed evidence that enough minoxidil is absorbed to have systemic effects, greater absorption due to misuse, individual variability or unusual sensitivity could, at least theoretically, produce a systemic effect.
Experience with oral minoxidil has shown the following major cardiovascular effects (Review the package insert for LONITEN® Tablets for details):
—salt and water retention, generalized and local edema
—pericardial effusion, pericarditis, tamponade
—tachycardia
—increased incidence of angina or new onset of angina
Patients with underlying heart disease, including coronary artery disease and congestive heart failure, would be at particular risk of these potential effects. Additive effects could also emerge in patients being treated for hypertension.
Potential patients should have a history and physical, should be advised of potential risks and a risk/benefit decision should be made. Heart patients should realize that adverse effects may be especially serious. Alert patients to the possibility of tachycardia and fluid retention, and monitor for increased heart rate, weight gain or other systemic effects.

PRECAUTIONS
General Precautions: Monitor patients one month after starting ROGAINE and at least every six months afterward. Discontinue ROGAINE if systemic effects occur. The alcohol base will burn and irritate the eye. If ROGAINE reaches sensitive surfaces (eg, eye, abraded skin and mucous membranes) bathe with copious cool water.
Avoid inhaling the spray.
Do not use in conjunction with other topical agents such as corticosteroids, retinoids and petrolatum or agents that enhance percutaneous absorption. ROGAINE is for topical use only. Each mL contains 20 mg minoxidil and accidental ingestion could cause adverse systemic effects.
Decreased integrity of the epidermal barrier caused by inflammation or disease of the skin, eg, excoriations, psoriasis or severe sunburn, may increase minoxidil absorption.
Patient Information: A patient information leaflet is included with each package and in the full product information.
Drug Interactions: No drug interactions are known. Theoretically, absorbed minoxidil may potentiate orthostatic hypotension in patients taking guanethidine.
Carcinogenesis, Mutagenesis and Impairment of Fertility: No carcinogenicity was found with topical application. Oral administration may be associated with an increased incidence of malignant lymphomas in female mice and hepatic nodules in male mice. In rats, there was a dose-dependent reduction in conception rate.
Pregnancy Category C: ROGAINE should not be used by pregnant women.
Labor and Delivery: The effects are not known.
Nursing Mothers: ROGAINE should not be administered.
Pediatric Use: Safety and effectiveness have not been established under age 18.

ADVERSE REACTIONS
ROGAINE was used by 3510 patients in placebo-controlled trials. Except for dermatologic events, no individual reaction or reactions grouped by body systems appeared to be increased in the minoxidil-treated patients.
Respiratory (bronchitis, upper respiratory infection, sinusitis) 5.95%, **Dermatologic** (irritant or allergic contact dermatitis) 5.27%; **Gastrointestinal** (diarrhea, nausea, vomiting) 3.42%; **Neurology** (headache, dizziness, faintness, light-headedness) 2.56%; **Musculoskeletal** (fractures, back pain, tendinitis) 2.17%, **Cardiovascular** (edema, chest pain, blood pressure increases/decreases, palpitation, pulse rate increases/decreases) 1.28%, **Allergy** (non-specific allergic reactions, hives, allergic rhinitis, facial swelling and sensitivity) 1.03%, **Special Senses** (conjunctivitis, ear infections, vertigo) 0.94%, **Metabolic-Nutritional** (edema, weight gain) 0.60%; **Urinary Tract** (urinary tract infections, renal calculi, urethritis) 0.46%, **Genital Tract** (prostatitis, epididymitis) 0.46%; **Psychiatric** (anxiety, depression, fatigue) 0.28%, **Hematology** (lymphadenopathy, thrombocytopenia) 0.23%, **Endocrine** 0.09%.
Patients have been followed for up to 5 years and there has been no change in incidence or severity of reported reactions. Additional events reported since marketing include: eczema, hypertrichosis, local erythema, pruritus, dry skin/scalp flaking, sexual dysfunction, visual disturbances including decreased visual acuity, exacerbation of hair loss, alopecia.

DOSAGE AND ADMINISTRATION
Hair and scalp should be dry before application. 1 mL should be applied to the total affected areas twice daily. Total daily dose should not exceed 2 mL. If the fingertips are used to facilitate drug application, wash the hands afterwards.

HOW SUPPLIED
60 mL bottle with multiple applicators NDC 0009-3367-05
Caution: Federal law prohibits dispensing without a prescription.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 22)

March 4-9—**11th Annual Mammoth Mountain Emergency Medicine Ski Conference.** UCI at Mammoth Lakes. Sun-Fri. 18 hrs. $395. Contact: Medical Conferences Inc, PO Box 52 B, Newport Beach 92662. (714) 650-4156.

March 19-23—**Emergency Medicine Symposium II.** UCSD at La Jolla Marriott Hotel. Mon-Fri. 32 hrs. Contact: UCSD.

March 21-23—**Advances in Emergency Medicine 1990.** UCSF at Mark Hopkins Hotel, San Francisco. Wed-Fri. 22 hrs. $425. Contact: UCSF.

April 7-14—**Cardiopulmonary Emergencies.** American Postgraduate Institute of Postgraduate Education and Scripps Memorial Hospital Encinitas at Poipu Beach Hotel & Waiohai Resort, Kauai, Hawaii. One week. Contact: Edith S. Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

April 19-22—**9th Annual Emergency Medicine and Acute Care: A Critical Appraisal, Series 3.** Emergency Medical Abstracts at San Francisco. Thurs-Sun. 20 hrs. Contact: Robert Cowsill, 6917 Royer Ave, West Hills 91307. (818) 884-8844.

May 7-11—**Emergency Medicine Symposium I: Cardiology, Pulmonary, Neurology.** UCSD at San Diego Hilton Beach and Tennis Resort. Mon-Fri. 32 hrs. $450. Contact: UCSD.

June 25-29—**Emergency Medicine Symposium III: Pediatrics.** UCSD at San Diego Hilton Beach and Tennis Resort. Mon-Fri. 32 hrs. $450. Contact: UCSD.

INTERNAL MEDICINE

January 18-21—**Advances in Gastroenterology.** UCSD at Hotel Del Coronado, San Diego. Thurs-Sun. 23 hrs. $425. Contact: UCSD.

January 19-20—**The Medical Dysphagia Team: From Intensive Care to Rehabilitation.** UCI at Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

January 25-27—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at Sheraton Grand Hotel, San Diego. Thurs-Sat. 17 hrs. $350. Contact: UCSD.

February 2-3—**7th Annual Reider Laser-Urology.** UCI at Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

February 3-4—**Searching for New Horizons in Non-Invasive Technology: The Next Decade.** UCSF at Union Square Holiday Inn, San Francisco. Sat-Sun. $200. Contact: UCSF.

February 9-10—**2nd Annual Bristol Myers Symposium on Neurosciences.** UCSD at Price Center, La Jolla. Fri-Sat. 12 hrs. $50. Contact: UCSD.

February 14-16—**23rd Annual Recent Advances in Neurology.** UCSF at Fairmont Hotel, San Francisco. Wed-Fri. 15 hrs. Contact: UCSF.

February 17-21—**Approaches to the Skull Base.** House Ear Institute at Marina Beach Hotel, Marina del Rey, Los Angeles. Sat-Wed. Contact: Antonio De La Cruz, MD, HEI, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

February 18-25—**Emergencies in Internal Medicine.** UCD at Lake Tahoe, Incline Village, Nevada. One week. 23 hrs. $410. Contact: UCD.

February 19-21—**Clinical Hematology and Oncology: 1990.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Wed. 24 hrs. $350. Contact: Bonny A. Mower, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

February 26-March 2—**Topics in Internal Medicine.** UCSD at Sheraton Harbor Island East Hotel, San Diego. Mon-Fri. 37 hrs. $475. Contact: Shirley Kolkey, 5665 Oberlin Dr, Ste 110, San Diego 92121. (619) 453-6222.

February 28-March 2—**10th Annual Current Approaches to Radiation Oncology, Biology and Physics.** UCSF at Hotel Nikko, San Francisco. Wed-Fri. 18 hrs. $325. Contact: UCSF Radiation Oncology Course, c/o Crest International, 940 Emmett Ave, Ste 14, Belmont 94002. (415) 595-2704.

March 5-6—**Advanced TMJ Arthroscopy: Rationale, Treatment, and Management.** UCSD. Mon-Tues. Contact: UCSD.

March 7-8—**Advances in Endocrinology and Metabolism.** UCSF at Fairmont Hotel, San Francisco. Wed-Thurs. 14 hrs. $275. Contact: UCSF.

March 15-17—**5th International Conference on Monoclonal Antibody Immunoconjugates for Cancer.** UCSD at Sheraton Harbor Island East, San Diego. Thurs-Sat. Contact: UCSD.

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April 18-20—**Advances in Infectious Diseases.** UCSD at Fairmont Hotel, San Francisco. Wed-Fri. 18 hrs. $380. Contact: UCSF.

April 21—**5th Annual Conference: New Treatments in Chronic Liver Disease.** Scripps Clinic and Research Foundation at Amphitheater of the Green Hospital, Scripps Clinic, La Jolla. Sat. $125. Contact: Bonny Mower, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 26—**Fine Needle Aspiration Tutorials.** UCSF. Sat. 7 hrs. Contact: UCSF.

June 4-5—**TMJ Arthroscopy: Rationale, Treatment, and Management.** UCSD. Mon-Tues. Contact: UCSD.

OB/GYN

January 18-20—**Liability in Perinatal Medicine: Prevention and Defense.** American College of OB/GYN at Carlsbad. Thurs-Sat. 16 hrs. $515. Contact: ACOG, 409 12th St SW, Washington, DC 20024-2188. (202) 638-5577.

January 28-February 2—**OB/GYN Update: 1990.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. 24 hrs. $395. Contact: UCD.

February 2-3—**7th Annual Reider Laser-Gynecology.** UCI at Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

February 15-18—**45th Annual Obstetrical and Gynecological Assembly of Southern California.** Ob-Gyn Assembly of California at Beverly Hilton, Beverly Hills. Thurs-Sun. 22 hrs. Contact: Director of Medical Education, 5820 Wilshire Blvd, No. 500, Los Angeles 90036. (213) 937-5514.

March 21-23—**Advanced Fetal Heart Rate Monitoring.** UCI at Newport Marriott Hotel, Newport Beach. Wed-Fri. Contact: UCI.

March 22-24—**Geriatric Gynecology With Special Emphasis on Urinary Incontinence.** UCI at Palm Springs. Thurs-Sat. Contact: UCI.

April 19-20—**Prenatal Genetics Diagnosis and Fetal Therapy.** UCI at Red Lion Hotel, Costa Mesa. Thurs-Fri. Contact: UCI.

April 28—**Symposium on Gynecologic Oncology.** Scripps Clinic and Research Foundation at La Jolla. Sat. 7 hrs. Contact: Bonny Mower, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

June 1-3—**Advanced Fetal Heart Rate Monitoring.** UCI at Monterey Plaza Hotel. Fri-Sun. Contact: UCI.

OPHTHALMOLOGY

January 28-February 1—**Squaw Valley Vitreo-Retinal Symposium.** UCD at Squaw Valley Inn, Olympic Valley. Sun-Thurs. 16 hrs. Contact: Barbara Arnold, MD, 7275 E Southgate Dr, Sacramento 95823. (916) 393-1000.

February 2-3—**Advances in Glaucoma Therapy.** UCSD at Sheraton Grande Torrey Pines, La Jolla. Fri-Sat. Contact: UCSD.

February 23-25—**American Academy of Ophthalmology Regional Update Course.** American Academy of Ophthalmology at Los Angeles. Fri-Sun. Contact: Gary Holland, MD, 655 Beach St, PO Box 7424, San Francisco 94120-7424. (415) 561-8500.

March 31—**Ocular Inflammation.** Scripps Clinic and Research Foundation at La Jolla. Sat. 8 hrs. $90. Contact: Susan Buntjer, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

PEDIATRICS

January 17-20—**Health Science Response to Child Maltreatment 1990.** Children's Hospital and Health Center at U.S. Grant Hotel, San Diego. Wed-Sat. Contact: Children's Hospital and Health Center, (619) 576-4072.

February 1-2—**Advanced Pediatric Emergencies: The First Three Hours.** Memorial/UCI Center for Health Education. Thurs-Fri. 8 hrs. Contact: UCI.

February 2-4—**Current Concepts in Pediatric Medicine 1990.** Children's Hospital at Hyatt Islandia, San Diego. Fri-Sun. Contact: Children's Hospital and Health Center, Medical Education Dept, 8001 Frost St, San Diego 92123. (619) 576-4072.

February 16-18—**Pediatrics in Progress.** American Academy of Pediatrics at Hyatt Regency Embarcadero, San Francisco. Fri-Sun. 16 hrs. $220. Contact: AAP, CME Registration, PO Box 927, Elk Grove Village, IL 60009-0927. (800) 433-9016.

March 30-31—**Neurodevelopmental Assessment of 4-9 Year Old Children.** Children's Hospital Oakland. Fri-Sat. 12 hrs. $150. Contact: Kim Leadon, Children's Hospital Oakland, 747 52nd St, Oakland 94609. (415) 428-3021.

April 6-7—**Annual Ambulatory Pediatrics.** UCD at Hilton Inn, Sacramento. Fri-Sat. Contact: UCD.

April 19-20—**9th Annual Child Abuse.** UCD at Radisson Hotel, Sacramento. Thurs-Fri. Contact: UCD.

June 29-30—**Current Concepts in Pediatric Allergy and Otolaryngology.** Children's Hospital San Diego at Hyatt Islandia Hotel, San Diego. Fri-Sat. Contact: Continuing Medical Education Office, Children's Hospital, (619) 576-4072.

PSYCHIATRY

January-May 1990—**Mental Research Institute Training Workshops at Mental Research Institute.** Contact: MRI, 555 Middlefield Rd, Palo Alto 94301. (415) 321-3055.

January 21-26—**16th Annual Midwinter Program for Psychiatrists.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. 25 hrs. $395. Contact: UCD.

January 29-February 2—**Introduction to Medical Hypnosis.** UCSD at The Inn at Del Mar. Mon-Fri. Contact: UCSD.

February 2-4—**Cognitive Therapy Conference.** University of Pennsylvania Cognitive Therapy and Research Department at Newporter Resort, Newport Beach. Fri-Sun. 16 hrs. Contact: Cass Jones, 7916 Convoy Court, San Diego 92111. (619) 565-9921.

February 9-11—**West Coast Psychiatry Board Review.** UCSD at Catamaran Resort Hotel, San Diego. Fri-Sun. 16 hrs. $450. Contact: Cass Jones, 7916 Convoy Court, San Diego 92111. (619) 565-9921.

February 24-25—**Basic Hypnosis: A Hands-On Workshop.** Southern California Society of Clinical Hypnosis at Airport Marina Hotel, Los Angeles. Sat-Sun. 12 hrs. $295. Contact: Karnie Starrett, 10840 Queensland St, Los Angeles 90034. (213) 475-1260.

March 16-19—**Advanced Medical Hypnosis.** UCSD at The Inn Rancho Santa Fe. Fri-Sun. Contact: UCSD.

April 23-27—**Introduction to Medical Hypnosis.** UCSD at The Inn at Del Mar. Mon-Fri. Contact: UCSD.

April 28-29—**The Cutting Edge 1990—The Heart of the Matter: Helping Improve Relationships.** UCSD at La Jolla Marriott Hotel. Fri-Sat. 13 hrs. $300. Contact: Cass Jones, 7916 Convoy Court, San Diego 92111. (619) 565-9921.

RADIOLOGY

January 19-21—**Advanced Imaging in Diagnostic Imaging.** UCSD at Ritz-Carlton Hotel, Laguna Niguel. Fri-Sun. Contact: UCSD.

January 26-28—**42nd Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 16 hrs. $395. Contact: LARS, PO Box 91215, Los Angeles 60009-1215. (213) 827-9078.

January 30-February 3—**16th Annual Mid-Pacific Radiological Conference.** Los Angeles Radiological Society at Maui Marriott Hotel, Maui, Hawaii. Tues-Sat. 16 hrs. $395. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078.

February 1-3—**Duplex Imaging.** UCSD at Le Meridien Hotel, San Diego. Thurs-Sat. 16 hrs. $375. Contact: UCSD.

March 2-4—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Resort Hotel, Laguna Niguel. Fri-Sun. 18 hrs. $400. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 5-7—**Neuroradiology Update.** UCSD at Hotel del Coronado, San Diego. Mon-Wed. 18 hrs. $375. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 5-9—**Combined Neuroradiology Update and Magnetic Resonance Imaging.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 29 hrs. $450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

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CONTINUING MEDICAL EDUCATION

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March 6-9—**Magnetic Resonance Imaging.** UCSD at Hotel del Coronado, San Diego. Tues-Fri. 23 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 6-9—**MRI for the Technologist: Symposium and Workshops.** UCSD at Hotel del Cornado, San Diego. Tues-Fri. 21 hrs. $275. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 16-18—**OB/GYN and Abdominal Sonography: Update 1989.** UCSF at Hyatt Regency, San Francisco. Fri-Sun. 15 hrs. $350. Contact: UCSF.

March 19-23—**33rd Annual Postgraduate Course in Diagnostic Radiology.** UCSF at Fairmont Hotel, San Francisco. Mon-Fri. 32 hrs. $515. Contact: UCSF.

March 26-30—**Diagnostic Imaging: 1990.** UCSF at Kauai, Hawaii. Mon-Fri. 23 hrs. $515. Contact: UCSF.

April 14-15—**MRI of the Musculoskeletal System.** UCSD at Hotel del Coronado, San Diego. Sat-Sun. 9 hrs. $175. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 15-20—**10th Annual San Diego Residents Radiology Review Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 39 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 21—**Introduction to Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Sat. 8 hrs. $100. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

May 22-25—**CT and MRI in Body Imaging: A Comprehensive Course.** Tues-Fri. 15 hrs. $515. Contact: UCSF.

SURGERY

January-December 1990—**Temporal Bone Surgical Dissection Courses: 1989.** House Ear Institute, 5 days per month. 53 hrs. $975. Contact: Antonio De la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

January-June 1990—**Microsurgery Training Courses.** UCSD at Grossmont Hospital, La Mesa. 40 hrs. $1125. Contact: UCSD.

January 19-20—**What's New in General Surgery: 12th Annual Postgraduate Course.** UCD at Capitol Plaza Holiday Inn, Sacramento. Fri-Sat. 14 hrs. $210. Contact: UCD.

January 19-21—**Southern California Chapter: American College of Surgeons.** American College of Surgeons at Four Seasons Biltmore, Santa Barbara. Fri-Sun. Contact: Laura Lee, (818) 708-3470.

January 22-26—**Oncology for the General Surgeon.** UCSD at Catamaran Resort Hotel. Mon-Fri. Contact: UCSD.

February 23—**Symposium on Retina and Vitreous Surgery.** White Memorial Medical Center New Otani Hotel and Garden, Los Angeles. Fri. 5 hrs. Contact: Farrah Arya, White Memorial Medical Center, 414 N Boyle Ave, Los Angeles 90033. (213) 269-0607.

March 15-18—**10th Annual San Diego Cardiothoracic Surgery Symposium: Pathophysiology and Techniques of Cardiopulmonary Bypass.** Cardiothoracic Research and Education Foundation at San Diego Marriott Hotel and Marina. Thurs-Sun. 17 hrs. $300. Contact: CREF, PO Box 33185, San Diego 92103. (619) 692-9115.

March 15-18—**Surgical Forum.** Society of Graduate Surgeons of Los Angeles County and USC Medical Center at Beverly Hilton, Beverly Hills. Thurs-Sun. Contact: Director, Society of Graduate Surgeons, 5820 Wilshire Blvd, Ste 500, Los Angeles 90036. (213) 937-5514.

April 7-8—**Automated Percutaneous Discectomy Workshop.** UCSF. Sat-Sun. 12 hrs. $800. Contact: UCSF.

May 16-20—**12th Annual: Wound Management Workshop.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sun. 19 hrs. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

June 21-23—**7th Annual San Diego Meeting on Arthroscopic Surgery of the Shoulder.** Tri-City Medical Center at La Jolla Marriott Hotel. Thurs-Sat. Contact: James C. Esch, MD, 3905 Waring Rd, Oceanside 92056. (619) 598-0080.

OF INTEREST TO ALL PHYSICIANS

January 16-20—**Intensive Course in Geriatric Medicine and Board Review.** UCLA at Beverly Hilton Hotel, Beverly Hills. Tues-Sat. 40 hrs. $295. Contact: UCLA.

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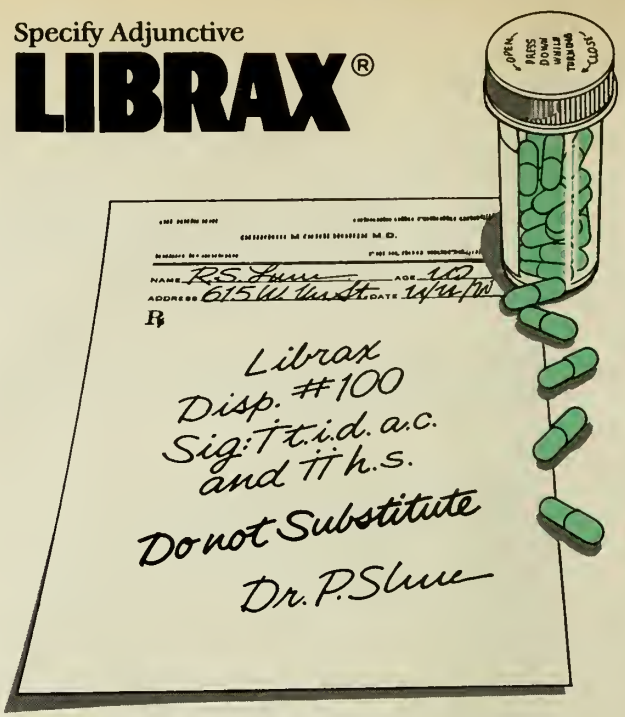
Specify Adjunctive

LIBRAX®



Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium bromide.

Please consult complete prescribing information, a summary of which follows:

* Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).
Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.
As with all anticholinergics, inhibition of lactation may occur.
Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).
Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.
Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.
Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of chlordiazepoxide; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. After extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

P.I. 0288

ROCHE® **Roche Products**

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Manati, Puerto Rico 00701

Be sure to specify Librax, "Do not Substitute" or your state's equivalent statement on your prescription.

In IBS,* when it's brain versus bowel,

IT'S TIME FOR THE PEACEMAKER.

In irritable bowel syndrome,* intestinal discomfort will often erupt in tandem with anxiety—launching a cycle of brain/bowel conflict. Make peace with Librax. Because of possible CNS effects, caution patients about activities requiring complete mental alertness.

*Librax has been evaluated as possibly effective as adjunctive therapy in the treatment of peptic ulcer and IBS.

Specify Adjunctive

LIBRAX®

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium bromide.

ROCHE

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Please see summary of prescribing information on adjacent page.

CONTINUING MEDICAL EDUCATION

(Continued from Page 28)

January 20—**Pediatric Cardiology for the Primary Physician.** Children's Hospital Oakland at Merritt Peralta Health Education Center, Oakland. Sat. 6 hrs. $110. Contact: Kim 1. Leadon, 747 52nd St, Oakland 94609. (415) 428-3021.

January 20-27—**Update: Controversies in Emergency and Primary Care.** American Institute of Postgraduate Education at Kona Surf Resort, Kona, Hawaii. 1 week. 21 hrs. $395. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

January 21-25—**Family Practice: Caring and Curing.** Kauai Foundation for Continuing Education and Hawaii Medical Association at Poipu Beach, Kauai. Sun-Thurs. 28 hrs. $450. Contact: David J. Elpern, MD, 3420-B Kuhio Hwy, Lihue, HI 96766. (808) 245-1173.

January 26-28—**Practical Aspects of Pain Management.** Hawaii Medical Association at Sheraton Kauai Hotel, Poipu, Kauai, Hawaii. Fri-Sun. 16 hrs. $275. Contact: John Dillon, MD, PO Box 457, Kalaheo, Hawaii 96741. (808) 742-6750.

January 26-28—**Pass or Fail? Examining Medical Education and Current Reforms.** Stanford University at Fairchild Auditorium. Fri-Sun. 15 hrs. $15. Contact: Doug Woelkers, (415) 725-2243.

January 27-28—**Pediatric Dermatology for the Primary Care Physician.** UCSF at Holiday Inn Union Square, San Francisco. Sat-Sun. 10 hrs. $205. Contact: UCSF.

February 1-3—**13th Neurology for Non-Neurologists.** UCSD at Holiday Inn Embarcadero, San Diego. Mon-Fri. 21 hrs. Contact: UCSD.

February 4-9—**CME Ski Meeting.** Nevada Academy of Family Physicians at Caesars Tahoe Stateline, Lake Tahoe, Nevada. Sun-Fri. 34 hrs. $395. Contact: Dotie Batchelor, PO Box 7471, Reno, NV 89510. (702) 826-5100.

February 5-9—**Occupational and Environmental Medicine III.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 40 hrs. $600. Contact: UCSF.

February 5-16—**Occupational and Environmental Medicine I.** UCSF at Cathedral Hill Hotel, San Francisco. 1½ weeks. 80 hrs. $1,200. Contact: UCSF.

February 7-9—**Clinical Laboratory Molecular Analysis.** Scripps Clinic and Research Foundation at San Diego Princess Resort. Wed-Fri. 21 hrs. Contact: Bonny A. Mower, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

February 9-10—**Infectious Disease.** UCD at Hilton Inn, Sacramento. Fri-Sat. 11 hrs. $165. Contact: UCD.

February 12-17—**UCI Family Practice Refresher Course.** UCI at Newport Sheraton Hotel, Newport Beach. Mon-Sat. Contact: UCI.

February 18-21—**Recent Advances in Geriatric Medicine: Strategies for Treating the Five Major Causes of Death and Disability in the '90s.** UCSD at Catamaran Hotel, San Diego. Sun-Wed. Contact: UCSD.

February 19-21—**10th Betty Ford Center Conference on Chemical Dependency.** Annenberg Center for Health Sciences and Betty Ford Center. Mon-Wed. Contact: Annenberg Center for Health Sciences at Eisenhower, 39000 Bob Hope Dr, Rancho Mirage 92270. (800) 321-3690.

February 19-23—**Physician Heal Thyself.** UCSD at San Diego Princess. Mon-Fri. 20 hrs. $350. Contact: UCSD.

February 22-24—**The Practicing Physician's Approach to Difficult Headache Patient.** Scripps Clinic and Research Foundation at Wyndham Hotel, Palm Springs. Thurs-Sat. 15 hrs. Contact: Idell Applebaum, 5252 N Western Ave, Chicago, IL 60625. (312) 878-5558.

February 24-25—**Advances in the Diagnosis and Treatment of Common Medical Problems.** UCSD at Sheraton Harbor Island East Hotel, San Diego. Sat-Sun. 12 hrs. $150. Contact: Shirley Kolkey, 5665 Oberlin Dr, Ste 110, San Diego 92121. (619) 453-6222.

March 2—**16th Annual Diabetes Symposium.** UCD at Hilton Inn, Sacramento. Fri. Contact: UCD.

March 2-7—**California Medical Association Annual Western Scientific Assembly.** California Medical Association at Disneyland Hotel, Anaheim. Fri-Wed. Contact: Sheri Sylvia, CMA, (415) 882-5184.

March 5-8—**Environmental Illness and Injury.** University of Nevada-Reno at Hyatt Lake Tahoe Resort, Incline Village, Nevada. Mon-Thurs. 14 hrs. $275. Contact: University of Nevada, Continuing Education Department, Reno, NV 89557. (702) 784-4046.

March 9-10—**Diabetes Update.** UCSF at Fairmont Hotel, San Francisco. Fri-Sat. 10 hrs. $225. Contact: UCSF.

March 12-15—**Critical Care Medicine: 28th Annual Symposium.** USC at Las Vegas Hilton, Nevada. Mon-Thurs. 27 hrs. $585. Contact: USC.

March 13-18—**Wilderness Medicine: '90.** American College of Emergency Physicians at Squaw Valley, Lake Tahoe. Tues-Sun. 22 hrs. $395. Contact: Eugene Allred, PO Box 321, Yreka 96097. (916) 842-4667.

March 19-22—**The Best Approach 1990: Effective, Efficient Strategies in Orthopaedics/Sports Medicine, Cardiology, Gynecology, and Infectious Disease.** Group Health Cooperative of Puget Sound at Intercontinental Hotel, Wailea, Maui, Hawaii. Mon-Thurs. 20 hrs. $325. Contact: GHCPS, CX-5, 201 16th Ave East, Seattle, WA 98112. (206) 326-6262.

March 24-25—**The Complaint of Insomnia in the Practice of Medicine: Scripps Clinic Sleep Update.** Scripps Clinic and Research Foundation. Sat-Sun. 11 hrs. $150. Contact: Susan Buntjer, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 28-30—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF at Hyatt Regency Hotel, San Francisco. Wed-Fri. 16 hrs. Contact: UCSF.

March 31-April 7—**Primary Care Medicine.** UCSF at Maui, Hawaii. One week. 20 hrs. $475. Contact: UCSF.

April 27—**Alzheimer's Update.** UCD at Beverly Garland Hotel, Sacramento. Fri. Contact: UCD.

June 11-15—**UCI Family Practice Refresher Course.** Memorial/UCI Center for Health Education at Westin South Coast Plaza, Costa Mesa. Mon-Fri. 29 hrs. Contact: UCI.

June 21-23—**Nevada State Medical Association Annual Meeting.** Nevada State Medical Association at Hyatt Lake Tahoe, Nevada. Thurs-Sat. Contact: Nevada State Medical Association, 3660 Baker Lane, Reno, NV 89509. (702) 825-6788.

IDAHO

July 26-28—**Idaho Medical Association—Annual Meeting.** Sun Valley. Thurs-Sun. Contact: Idaho Medical Association, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

January 15-19—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Fri. Contact: American Educational Institute, (800) 354-3507.

January 18-19—**Ocular Trauma.** Holiday Inn Pyramid Journal Center, Albuquerque. Thurs-Fri. Contact: Mary R. Boning, Office of Medical Education and Research at Presbyterian Hospital, (505) 841-1225.

January 20—**Neuropsychiatry.** Psychiatric Medical Association of New Mexico at University of New Mexico, Department of Nursing and Pharmacy, Albuquerque. Sat. Contact: Psychiatric Medical Assn, (505) 841-3511.

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Preventing Malpractice in Emergency Medicine: Case Studies

Sheraton at Fisherman's Wharf San Francisco, California
February 2-3, 1990

Co-sponsored by the California Chapter of ACEP

Bad Outcomes May Occur, Malpractice Need Not.

This 2 day course for physicians and risk managers in Emergency Medicine uses actual closed malpractice cases and relevant scientific literature to illustrate the most important and common pitfalls in the practice of Emergency Medicine. Critical components of the history, physical and data collection that are pivotal in assuring a well supported evaluation, assessment and treatment will be identified.

Also included:

- Medical-Legal issues in Emergency Department Activities
- Developing effective Quality Assurance Programs
- Issues in Medical Record Documentation
- Preparing for Deposition and Trial

This course has applied for 12 hours of ACEP Category I credit. Special hotel rates are available for course participants.

For course information and registration, contact:
Risk Management Programs
120 Montgomery Street, Suite 1000, San Francisco, CA 94104 (415) 433-RISK

Upcoming Presentations:	***June 11-14, 1990***	***Lake Tahoe, CA***
	August 28-31, 1990	***Honolulu, Hawaii***
	November 14-16, 1990	***Los Angeles, CA***

CONTINUING MEDICAL EDUCATION

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January 22-26—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Fri. Contact: American Educational Institute, (800) 354-3507.

February 5-9—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Fri. Contact: American Educational Institute, (800) 354-3507.

February 12-16—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Fri. Contact: American Educational Institute, (800) 354-3507.

February 19-23—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Fri. Contact: American Educational Institute, (800) 354-3507.

February 23-25—**18th Annual New Mexico Thoracic Society Lung Disease Conference.** Santa Fe. Fri-Sun. Contact: Billie Dytzel, American Lung Association of New Mexico, 216 Truman, NE, Albuquerque 87118. (505) 265-0732.

February 26-March 3—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Sat. Contact: American Educational Institute, (800) 354-3507.

February 28-March 3—**New Mexico Metabolism Symposium.** Taos. Wed-Sat. Contact: Kathy Sickes, Lovelace Medical Foundation, 2441 Ridgecrest Dr, SE, Albuquerque 87108. (505) 262-7749.

March 5-9—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Fri. Contact: American Educational Institute, (800) 354-3507.

March 10—**Update: Pediatric Hematology.** Albuquerque. Contact: Alfred Florman, MD, New Mexico Pediatric Society, Surge Building, UNM SOM, Albuquerque 87131. (505) 277-5551.

March 12-16—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Fri. Contact: American Educational Institute, (800) 354-3507.

March 14-18—**Sports Medicine for the Primary Care Physician.** Durango, Colorado. Wed-Sun. Contact: Kathy Sickes, Lovelace Medical Foundation, 2441 Ridgecrest Dr, SE, Albuquerque 87108. (505) 262-7749.

March 15-18—**Medicine in Transition—Apathy or Renewal?** Albuquerque. Contact: John R. Graham, MD, Albuquerque Centre for Psychotherapy, 7521 Lantern Rd, NE, Albuquerque 87109. (505) 883-6959.

March 17—**Illness Behavior.** Psychiatric Medical Association of New Mexico at University of New Mexico, Department of Nursing and Pharmacy, Albuquerque. Fri. Contact: Psychiatric Medical Assn, (505) 841-3511.

March 19-23—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Fri. Contact: American Educational Institute, (800) 354-3507.

March 26-30—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Fri. Contact: American Educational Institute, (800) 354-3507.

March 30-31—**Can OB/GYN Survive Liability?** Albuquerque Convention Center. Fri-Sat. Contact: Mary R. Boning, Office of Medical Education and Research, Presbyterian Hospital, (505) 841-1225.

April 2-6—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Fri. Contact: American Educational Institute, (800) 354-3507.

April 9-13—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Fri. Contact: American Educational Institute, (800) 354-3507.

May 4-5—**103rd Annual Meeting of the New Mexico Medical Society.** Albuquerque. Fri-Sat. Contact: Glenn Taylor, New Mexico Medical Society, 7770 Jefferson, NE, Albuquerque 87109. (505) 828-0237.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 31)

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

(Continued on Page 34)

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How to Register

ACP Members: complete the registration form found in the back of the Advance Program you received in December.

Non-members: look for the complete schedule of events and a registration form in the 12-page insert appearing in the December 1 and February 1 issues of *Annals of Internal Medicine,* or call 1-800-523-1546 (extension 2429). In Pennsylvania and outside the U.S., call 215-351-2429.

Pre-registration deadline: March 19, 1990.

WJM

American College of Physicians Independence Mall West Sixth Street at Race Philadelphia, PA 19106-1572

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* * *

January 13-20—**Special Problems in Athletic Injuries and Trauma** (Sponsor: UUMC). Sat-Sat. Prospector Square, Park City. Contact: (801) 581-8664.

January 24-28—**The Immunocompromised Surgical Patient: Mechanisms and Therapy in Burns and Trauma** (Sponsor: UUMC). Wed-Sun. Snowbird. Contact: (801) 581-8664.

February 5-9—**Sixth Annual Surgical Pathology Ski Retreat** (Sponsor: UUMC). Mon-Fri. The Yarrow, Park City. Contact: (801) 379-7178.

February 10-17—**Update in Clinical Microbiology and Immunology** (Sponsor: UUMC). Sat-Sat. The Yarrow, Park City. Contact: (801) 581-7480.

February 13-16—**Family Practice Refresher Course** (Sponsor: UUMC). Tues-Fri. Salt Lake Hilton, Salt Lake City. Contact: (801) 581-8635.

February 16-20—**Thirty-Fifth Annual Anesthesiology Update** (Sponsor: UUMC). Fri-Tues. Snowbird. Contact: (801) 581-6115.

February 17-21—**Thirty-First Annual Ob/Gyn Update** (Sponsor: UUMC). Sat-Wed. The Yarrow, Park City. Contact: (801) 581-5501.

February 21-23—**Physical Medicine and Rehabilitation Update** (Sponsor: UUMC). Wed-Fri. Park City. Contact: (801) 584-1226.

February 21-24—**Teratology for the Practitioner** (Sponsor: UUMC). Wed-Sat. Park City. Contact: (801) 581-5501.

February 21-24—**Pediatric Emergency Medicine** (Sponsor: UUMC). Wed-Sat. Salt Lake City Marriott, Salt Lake City. Contact: (801) 521-1315.

March 5-9—**Advances in Internal Medicine** (Sponsor: UUMC). Mon-Fri. Snowbird. Contact: (801) 581-8664.

March 11-16—**Wilderness Medicine** (Sponsor: UUMC). Sun-Fri. Snowbird. Contact: (801) 581-8664.

May 3-4—**Ethics and Health** (Sponsor: UUMC). Thurs-Fri. University of Utah Health Science Center, Salt Lake City. Contact: (801) 581-8664.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

January 17—**Automotive Medicine.** Seattle. Wed. Contact: Northwest Hospital, (206) 364-0500.

January 18—**Law & Medicine Symposium.** Tacoma. Thurs. Contact: PCMS, (206) 627-7137.

January 19—**13th Annual Cardiology Conference.** Everett. Fri. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

January 24-26—**Modern Molecular Biology for Physicians.** Seattle. Wed-Fri. Contact: U/W.

February 1-3—**Medical and Surgical Management of Heart Disease.** Seattle. Thurs-Sat. Contact: U/W.

February 2—**Peripheral Vascular Disease, 1990.** Seattle. Fri. Contact: VMMC.

February 8-9—**Cancer Review 1990.** Tacoma. Thurs-Fri. Contact: PCMS, (206) 627-7137.

February 8-10—**Ophthalmology: Annual President's Meeting.** Seattle. Thurs-Sat. Contact: (206) 441-9762.

February 9-10—**Cardiology Conference.** Seattle. Fri-Sat. Contact: VMMC.

February 11-13—**Critical Care.** Crystal Mountain. Sun-Tues. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

February 21—**Neurology.** Seattle. Wed. Contact: Northwest Hospital, (206) 364-0500.

February 28—**AIDS Update.** Tacoma. Wed. Contact: PCMS, (206) 627-7137.

March 3—**AIDS Issues '90.** Kirkland. Sat. Contact: Evergreen Hospital, (206) 823-7599.

March 8-9—**Tacoma Academy of Internal Medicine Annual Review.** Tacoma. Thurs-Fri. Contact: CME Pierce County.

March 9—**Risk and Insurance Management for Physicians in Practice.** Seattle. Fri. Contact: VMMC.

March 15-16—**Primary Care Orthopaedics.** Seattle. Thurs-Fri. Contact: U/W.

March 21—**Drugs.** Seattle. Wed. Contact: Northwest Hospital, (206) 364-0500.

March 21-23—**Recent Advances in Cancer Detection.** Seattle. Wed-Fri. Contact: U/W.

March 26-April 6—**Physical Medicine and Rehabilitation.** Bellevue. Mon-Sun. Contact: U/W.

March 29-31—**Trauma and the Elderly.** Seattle. Thurs-Sat. Contact: U/W.

April 6—**A Day of Infectious Disease.** Seattle. Fri. Contact: VMMC.

April 12—**Psychopharmacology.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

April 13-14—**Tacoma Surgical Club.** Tacoma. Fri-Sat. Contact: (206) 627-7137.

April 27—**Dermatology.** Tacoma. Fri. Contact: (206) 627-7137.

May 4-5—**Orthopedic Review.** Seattle. Fri-Sat. Contact: VMMC.

May 10—**Nutrition.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

May 10-11—**Aggressive Musculoskeletal and Spinal Evaluation, Treatment, and Rehabilitation.** Tacoma. Thurs-Fri. Contact: CME Pierce County.

May 18-19—**Applications of Doppler Ultrasound.** Seattle. Fri-Sat. Contact: VMMC.

June 8-9—**Common Anorectal Disorders: A Medical and Surgical Approach.** Seattle. Fri-Sat. Contact: VMMC.

June 14-15—**Orthopaedics.** Seattle. Thurs-Fri. Contact: Northwest Hospital, (206) 364-0500.

June 16—**AIDS Issues 1990.** Kirkland. Sat. Contact: Evergreen Hospital, (206) 823-7599.

June 25-26—**Advanced Cardiac Life Support.** Tacoma. Mon-Tues. Contact: CME Pierce County.

WYOMING

February 25-March 3—**Wyoming Academy of Family Physicians Annual Ski Meeting and Family Practice Update.** Jackson Hole. Sun-Sat. Contact: Hughes Planning, PO Box 3556, Jackson 83001. 1 (800) 342-7526.

June 14-16—**Wyoming Medical Society—Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sat. Contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. ◆

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Reversible confusional states have been observed on occasion, predominantly in severely ill patients.

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However, a crossover study in healthy subjects receiving either 'Tagamet' 300 mg q.i.d. or 800 mg h.s. concomitantly with a 300 mg b.i.d. dosage of theophylline (Theo-Dur®, Key Pharmaceuticals, Inc.) demonstrated less alteration in steady-state theophylline peak serum levels with the 800 mg h.s. regimen, particularly in subjects aged 54 years and older. Data beyond ten days are not available. (Note: All patients receiving theophylline should be monitored appropriately, regardless of concomitant drug therapy.)

In a 24-month toxicity study in rats, at dose levels approximately 8 to 48 times the recommended human dose, benign Leydig cell tumors were seen. These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving 'Tagamet'.

A weak antiandrogenic effect has been demonstrated in animals. In human studies, 'Tagamet' has been shown to have no effect on spermatogenesis, sperm count, motility, morphology or in vitro fertilizing capacity.

Pregnancy Category B: Reproduction studies have been performed in rats, rabbits and mice at doses up to 40 times the normal human dose and have revealed no evidence of impaired fertility or harm to the fetus due to 'Tagamet'. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Lack of experience to date precludes recommending 'Tagamet' for use in children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should not be undertaken by patients taking the drug since cimetidine is secreted in human milk.

Adverse Reactions: *Diarrhea, dizziness, somnolence, headache. Reversible confusional states (e.g., mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation), predominantly in severely ill patients, have been reported. Reversible impotence in patients with pathological hypersecretory disorders receiving 'Tagamet', particularly in high doses for at least 12 months, has been reported. The incidence of impotence in large-scale surveillance studies at regular doses has not exceeded that commonly reported in the general population. Gynecomastia has been reported in patients treated for one month or longer. Decreased white blood cell counts in 'Tagamet'-treated patients (approximately 1 per 100,000 patients), including agranulocytosis (approximately 3 per million patients), have been reported, including a few reports of recurrence on rechallenge. Most of these reports were in patients who had serious concomitant illnesses and received drugs and/or treatment known to produce neutropenia. Thrombocytopenia (approximately 3 per million patients) and, very rarely, cases of aplastic anemia have also been reported. Increased serum transaminase has been reported. Reversible adverse hepatic effects, cholestatic or mixed cholestatic-hepatocellular in nature, have been reported rarely. Because of the predominance of cholestatic features, severe parenchymal injury is considered highly unlikely. A single case of biopsy-proven periportal hepatic fibrosis in a patient receiving 'Tagamet' has been reported. Increased plasma creatinine has been reported. Rare cases of fever, interstitial nephritis, urinary retention, pancreatitis and allergic reactions, including anaphylaxis and hypersensitivity vasculitis, have been reported. Rare cases of bradycardia, tachycardia and A-V heart block have been reported with H_2-receptor antagonists. Reversible arthralgia, myalgia and exacerbation of joint symptoms in patients with preexisting arthritis have been reported rarely. Rare cases of polymyositis have been reported, but no causal relationship has been established. Mild rash and, very rarely, cases of severe generalized skin reactions (e.g., Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis and generalized exfoliative erythroderma) have been reported with H_2-receptor antagonists. Reversible alopecia has been reported very rarely.*

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Journal of the Arizona Medical Association

ARIZONA MEDICINE

January 1990, Vol. XLVII, No. 1

Why Me, Daddy?

Marshall B. Block, M.D.

During a recent family bicycle outing one of my daughters sustained a fall unfortunately resulting in a bimalleolar fracture. As she lay on the sidewalk in pain, she looked into my eyes and asked "Why me, Daddy?" Then, as now, I did not have a ready answer. Things happen in life for which we have no explanations. It is not surprising, therefore, that in medicine similar things occur. However, in our circumstances we are expected to have answers. When we don't, patients accuse us of not exercising enough diligence ("You missed the diagnosis!") or we feign not knowing enough ("It is out of my area of expertise") or worse yet we are accused of somehow being responsible for the occurrence in the first place ("It started right after I took that antibiotic!").

Most of these episodes have no readily discernible causative agent and run their own course with or without our therapeutic intervention. However, we feel somehow compelled to find the cause and when we don't we tend to transfer the causation to the patient.

"Could it be emotional?" is a remark that attempts to transfer responsibility from "medicine" to the patient. On many occasions stressful life circumstances can cause physical problems. But even if this is true, producing the dichotomy of "us versus them" is many times not therapeutic. It pits patient against physician rather than aligning us. We are viewed as foe rather than a friend. Perhaps that is why so many people have "hypoglycemia," "P.M.S.," "mitral valve prolapse," "Barr-Epstein viral syndrome" or even lately "Lyme disease." However, finding a disease for the patient's complaints is not necessarily the "best medicine" as it does not deal with the underlying cause of their problems. What then to do? How best to handle this kind of situation?

Obviously, each patient is unique and can handle the same information differently. I am continually amazed at the lack of insight patients have in regard to their underlying conflicts. Our society has fostered a physical basis for most of our difficulties which has been perpetuated by us in many guises ("Let's make sure there is nothing physically wrong"). What we need to do is bite the bullet and approach these problems honestly with the patient. This takes time and requires carefully constructed words so as not to make an already frightened patient more alarmed or worse yet, angered. The art of medicine is needed at these times to help patients deal with the fear of the unknown. "Why me, Daddy?" is a call for help and support, even if we don't have the answers. The uncertainty <u>we</u> feel in these circumstances is matched by that which the patient is experiencing. Perhaps by combining forces we can deal with these temporary setbacks more effectively. ■

Marshall B. Block, M.D., Editor

Journal of the Arizona Medical Association

ARIZONA MEDICINE

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- Disability Insurance Policy
- Tactics Used by Plaintiff Attorneys
- To Contract or Not to Contract
- Gleanings from ArMA's Past
- Physicians in the News
- HCPCS Coding
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Thomas J. Marks

Computers 1990

We all know computers are a major part of our lives. The changes in the '80s were as dramatic as the influx of the regulatory environment on the medical profession. Computers which used to fill whole rooms now fit conveniently on the office manager's desktop. What effect will this have on the practicing physician as he/she positions for the 90s?

Price Performance Ratios

The changes here are as spectacular as in any industry. Does anyone remember $1,000 microwaves? The same holds true for office-based computers. $45,000 of purchased computer power in 1983 can now be bought for $15,000. Prices are down...performance is up. A PC-386 can handle the most demanding of office-based applications, including billing, CPT-coding, etc. With the advent of the new 486s, prices are destined to fall even further. Physicians re-entering the market place for new or upgraded systems need to educate themselves more than ever as to what constitutes raw computing power. It's important to balance price, maintenance, ease of use and upgraded path. A more expensive system is not necessarily better if you or your staff can't extract the information you need. There have been many instances where the cost of maintenance and custom software have far exceeded the cost of the hardware.

Online Communications

It is staggering the amount of useful information available not only for the practicing physician but for the physician's other interests as well. In 1989 the ArMA leadership committed to implement an online communication system. At any time, day or night, they can communicate on the message board eliminating phone tag. Additionally, up-to-minute information from the AMA,Washington and Arizona Legislature, calendars, etc., can be viewed.

The ability to conference with others on ArMA's system will be implemented in 1990, thus enhancing its usefulness. Many other corporate online information services exist that can aid the physician in practice. Imagine that in one session you could check airline fares and weather for your upcoming vacation, run a demographic report to find out the best location for your next satellite office, and pull the latest report from the Center for Disease Control, all from the same service. Most of these services can be completely automated, thus allotting the physician more time for patient care.

This precursor will serve as an introduction to the many areas that will be addressed in the coming months. We will take an indepth look at communications, personal productivity software, front office and education programs. Specific hardware/software combinations will be viewed from a physician's perspective.

Thomas J. Marks
Director
Management Information Services

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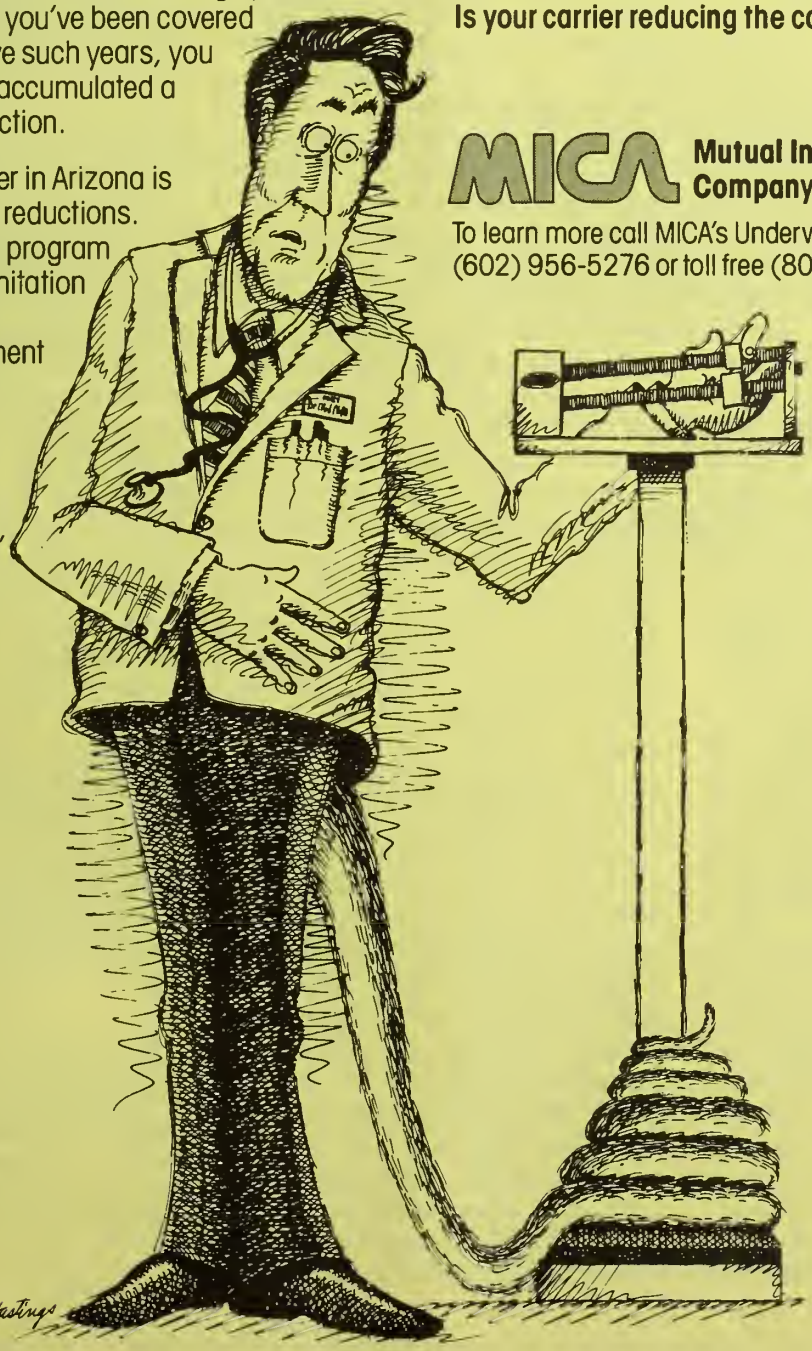

A Current Perspective on Some Commonly Referred Sleep Disorders

The past two decades have witnessed a phenomenal growth in the area of sleep disorders medicine, including the accreditation of sleep disorders centers and the certification of clinical polysomnographers widely across the country. This momentum of service availability has been paralleled by new insights into the pathogenesis of sleep disorders and by innovative treatments. We have chosen three conditions commonly referred to Sleep Disorders Centers to illustrate the advance of knowledge in this clinical field.

The tendency to develop narcolepsy appears to be hereditarily transmitted as a dual threshold multifactorial genetic condition, in which one group of individuals presents solely with excessive daytime sleepiness, and the other group with one or more other features of the tetrad. It is highly correlated with the HLA-DR2 antigen, in some studies reaching 100%. Retrospective studies have revealed that the onset of the disease is quite frequent in childhood or adolescence and it results in hyperactivity and serious impairment in scholastic performance. Yet, it is rarely, if ever, recognized at this time. Neurochemical studies suggest that narcolepsy is associated with a failure of dopamine release and with an upregulation of cholinergic receptors. These and other neuropharmacological observations should guide the clinician in selecting more rational and targeted symptomatic therapy in narcolepsy.

A second common sleep disorder, obstructive sleep apnea syndrome, is now recognized as an important clinical problem. Epidemiologic studies suggest that the prevalence may be as high as 1% of the general adult population. Furthermore, its impact on public health can no longer be ignored. Individuals with symptomatic sleep apnea are eight times more likely to have a motor vehicle accident and are five times more likely to die from myocardial infarction or stroke. Physiologic studies have led to an increased understanding of the pathogenesis of this disorder. In comparison to non-apneic individuals, patients with sleep apnea have a narrower and more compliant pharyngeal airway. Furthermore, sleep apnea patients are more likely to have abnormalities in ventilatory control.

Treatment for patients with obstructive sleep apnea is no longer limited to tracheostomy. The introduction of compact, portable, and relatively comfortable nasal continuous positive airway pressure units (CPAP) has revolutionized therapy for this disorder. With this device, symptoms of sleep apnea can be abolished literally overnight. Although initially quite promising, uvulopalatopharyngoplasty has been shown to be of inconsistent benefit with only 50% of operated patients having substantial improvement in their apnea. New treatment modalities such as transtracheal oxygen and dental mandibular advancement appliances recently have been introduced and may be viable therapeutic options in the future.

In the past few years, there has been rapid advancement in the understanding and treatment of a third common sleep disorder, persistent insomnia. A thorough diagnostic assessment is necessary because there are many variables that can contribute to poor sleep including physical illness, aging, drugs, psychological problems, poor sleep habits, and circadian rhythm disturbances. An all-night polysomnogram can exclude other contributing sleep disorders such as sleep apnea, periodic movements, and restless legs.

Hypnotics should be avoided for persistent insomnia as they are ineffective for chronic problems and can produce drug-dependent insomnia, increased respiratory problems, dysphoric mood, and impaired motor and intellectual functioning. In recent years considerable success has been achieved with behavioral treatments for insomnia such as stimulus control instructions in which the patient relearns to use the bed and bedroom as cues for sleep, relaxation training for reducing daytime tension, and light therapy in which bright light is used to shift the patient's sleep-arousal circadian rhythm.

Ongoing research into these and other sleep disorders has yielded a breadth of knowledge that has been recognized as being sufficiently challenging to justify a new specialty in Sleep Disorders Medicine. This is being actively considered. ■

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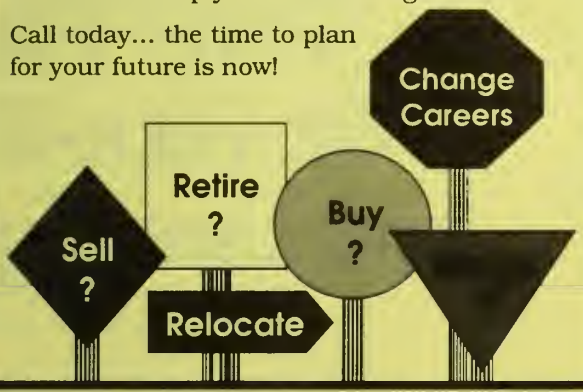

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Does Your Disability Policy Cover You On Take-Off and Landing?

Ken Davis, CPA, CFP

What does take-off and landing have to do with disability insurance? Keep reading and I'll show you.

Let's assume for the moment that you buy a $2,000,000 airplane. You buy an accident insurance policy on the plane to protect your $2,000,000 investment. You had asked all your flying buddies what to buy. They all recommended you use the policy you bought because it was the cheapest. A month later the landing gear on your airplane freezes and you crash land. Thank goodness everybody gets out safely but the plane is totally ruined. The next day you call the insurance company to file your $2,000,000 claim. The insurance company gathers the facts and informs you that you are not covered because you landed between 3:00 P.M. and 6:00 P.M. on the day of the crash. That time of the day is not covered because that is the busiest time of the day. Your low cost insurance policy does not cover this time period so that the company can keep your rates down. You are irate! You paid good money for insurance only to find out you are not covered. You rush to the file cabinet and pull out the contract. At first you read the contract and it says all accidents are covered. Looking further you find that there are several exceptions to the general rule. One of them is the time constraint the insurance company quoted. You now know you have lost a great deal of money with no way to recoup your loss. What a tragedy!

Much later after the anger passed you asked yourself what happened. You realize you trusted your friends' well intentioned but unprofessional judgement and bought the cheapest coverage on the market.

Could a similar situation happen with your disability insurance when you land in bed disabled? You bet it can! ***We review a lot of disability contracts for our member doctors. We frequently find subtle contract terms that are like potholes in the runway. They are hard to see up above but they cause a lot of damage when you try to land!***

I picked the airplane analogy because a plane is a tangible asset and it is easy to see how it can be damaged. It is completely accepted that accident coverage on an expensive asset is mandatory. Disability coverage is harder to relate to, for some of you, because your ability to work is an intangible asset. In most cases your ability to work is at least as valuable as the $2,000,000 airplane! For instance, if you make $200,000 a year, then a loss of just 10 year's earnings is a $2,000,000 loss. Don't you agree that you are worth ***at least*** $2,000,000? Can you afford to buy weak coverage for your most important asset!

At this point you may be thinking that all policies are bad and that insurance is just another scam. The fact is that insurance contracts come in all kinds of shapes and sizes. Yes, there are bad contracts and weak insurance companies. The bigger problem, as I see it, is an incompetent insurance agent selling insurance to an uninformed buyer.

A competent agent can prescribe the right contract for a particular situation while keeping costs down for his client (a good agent will stay away from weak companies). For example, in our above story the insurance policy might have been appropriate for an owner that never flew his plane during the policy restricted times and needed a break on his premiums. In that case the policy owner only pays for what he needs. There is nothing sinister about the policy sold in our fictional account. Instead, it was tragic that a policy, useful in some circumstances, was sold to the wrong client.

While it is true that you get what you pay for, it is also true that you can still shop around for a better price. The key is to focus in on the terms of the contract and the strength of the insurance company first; then the price. The contract terms in a disability policy are too complex and varied to discuss in an article like this. However, we are always available to consult with ArMA members to review and discuss their policies and to help them avoid costly errors!

Why use ArMA Membership Benefits, Inc. to review your disability situation? Well, here at ArMA Membership Benefits, Inc. we are employees of a company which is a wholly-owned subsidiary of the Arizona Medical Association. We are held accountable to you by a board of directors made up primarily of M.D.s who share the same concerns as you. Also, every time you buy your insurance through us you pay yourself dividends. That is because the profits of the subsidiary go to the Association and are returned to you in the form of additional services. Finally, we believe the people employed by ArMA Membership Benefits, Inc. are highly qualified professionals.

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Caution: Beware of Tactics Used by Plaintiff Attorneys!

Most lawyers take depositions in a straightforward, direct manner and seldom resort to tricks or gimmicks. However, a few lawyers can't seem to ask straight questions. If you understand a trick question, you will have little trouble in dealing with it. The following are typical examples of trick questions.

1. The shell game question. In this ploy the lawyer attempts to shift dates, places or subjects without advising the witness. If the lawsuit involves two transactions, he may start the witness talking about transaction number one and then, without alerting the witness, skillfully weave in a few questions which could only relate to transaction number two. For instance, if the lawyer wants to imply that the doctor had knowledge of a patient's allergy before he administered certain medication, he may start with questions concerning a conversation which took place before the injection, and then skillfully work in questions concerning the witness's knowledge of the reaction after the injection, without reference to the time lapses. You may respond to such questions with a request for clarification of the time, place or subject, or you may answer the questions pointing out the difference in time.

2. The sham question. This question sounds something like this: "You know, of course, that drug X is dangerous." This is not a question but a statement made so emphatically that the witness is almost compelled to agree. Drug X may not be dangerous at all. Indeed, it may be the safest product of its kind on the market. The proper answer to this question might be: "No, I don't believe it is dangerous at all."

This is a form of leading question. A leading question is one in which the lawyer suggests the answer he wants. It usually appears as more of a statement than a question: "You didn't actually see the x-ray very clearly, did you?" Remember to think for yourself. Don't let the question put words in your mouth. Your reply may be: "I saw it very clearly."

3. The vain Caesar question. This question plays on the witness's vanity and sounds something like: "As a surgeon, don't you know that some infection will always result from this type of surgery?" The inference is that the witness is a bad surgeon becase he didn't know the possible results. You would be amazed at the number of people who readily admit to knowing non-existent facts for vanity's sake. The correct answer might have been "no" or "No, infections will not always occur."

4. The "you said it" question. Sometimes lawyers misquote a witness's prior testimony. Misquoting a witness can be intentional or unintentional. In either event, the witness should immediately correct the lawyer in a polite but firm manner such as "I am sorry, you must have misunderstood me, because I certainly did not say I am absolutely certain that he entered the intersection on a red light." Oftentimes, misquotations are more subtle. You may have testified that you observed a plaintiff's car traveling 50 to 60

miles an hour. Plaintiff's attorney may later ask: "Tell us where you were standing when you saw plaintiff's car traveling down the road at 50 miles an hour." The lawyer nicely shaved 10 miles an hour from your estimate. You may, if you choose, add the 10 miles an hour back in your answer.

Watch out for questions which appear to summarize or sum up your testimony. The lawyer's summary may be incomplete.

A doctor may have testified that he found a number of conditions which persuaded him not to operate on a patient. After lengthy testimony, the lawyer may ask: "Well now, Dr. Smith, is it your testimony that you decided not to operate because the patient was in shock?" No, that wasn't the doctor's testimony, and if that question and answer were read out of context to the jury, it would suggest that the doctor failed to operate for only one reason. The witness can protect against the chance that a jury will be misled by answering: "That is one of the reasons I decided not to operate."

Beware of summary questions which start out with such words as:

"Is it your testimony that . . ."

"If I understand you, then you are saying . . ."

"Are you telling us that . . ."

Make sure that your testimony is properly quoted. Correct the attorney if he misquotes you.

5. The "have you talked to anybody about this case" question. The lawyer who pulls this antique trick out of the hat usually puts on his most accusing manner and asks: "Have you discussed this case with your lawyer?" The answer to that question should be, "Certainly I have." Every juror knows that it would take a mighty stupid lawyer not to talk to a witness before putting him on the witness stand. The next question usually comes up: "Did he tell you what to say to the jury?" The witness: "he told me to tell the truth and to be as fair and accurate as I could be."

6. The "how much are you getting paid" question. This question usually directed toward expert witnesses and professional people who may be hired by an attorney to do research, conduct tests and appear in court. However, it can be directed to any witness. The question may be asked like this: "Doctor, how much did they pay you to come in here and testify that in your opinion, Mrs. Johnson was not hurt in the accident?" The tricky part of this question is that the witness was paid for his time, but not to testify in a certain manner. The correct answer to the question might be: "I wasn't paid a penny to testify that Mrs. Johnson wasn't hurt; that is my sincere and honest opinion. I was simply paid to examine her and for my time in appearing here to give the jury, as best I can, the results of my examinations."

7. The "how high is up" question. Beware of open-ended comparisons. By that I mean a question which asks: "Was it long?" A simple yes or no answer may lead to difficulty later on. Long is a relevant word. Long compared to what? A witness can respond by asking for clarification or he may simply state: "It was about 3 feet long."

8. The "have you stopped beating your wife" question. This is the classic "trick" question known to everyone. Of course, you cannot answer either yes or no without running into difficulty. The question can be asked in a variety of forms, such as, "Doctor, is it still your practice to use a surgical procedure which has been criticized by most authorities in your field?," or, in another context, "Mr. Engineer, is your company still manufacturing defective drill presses of the type which injured Mr. Plaintiff?" Of course, the attorney calling you should object to the question. However, if no objection is interposed, or if you are compelled to answer, the appropriate answer might be: "I cannot accept the premise of your question because that surgical procedure is the one recommended by the most reputable authorities in the field." Or, "The drill press which you described is one of the best designs on the market and certainly was not defective."

9. The "you could have done better" question. Plaintiff's lawyers know that no matter how skillfully and carefully the defendant has acted, there is always room for a higher degree of skill and care. If a doctor applied seven sutures to the wound, there is always the argument that it should have been eight. If the manufacturer installed a failsafe feature on the product, there is always the argument that there should have been a backup failsafe feature...or two...or three. Such issues can be faced in a straightforward series of questions and answers. However, some attorneys insist upon trying to put the witness in a box with argumentative questions.

10. The impossible question. There is an interesting difference between scientists and lawyers when they consider the word "impossible." To start with, scientists (engineers, doctors, etc.) think in terms of precise types of physical behavior and mathematical possibilities. Lawyers, on the other hand, often think in terms of how the evidence may appear to the jury. An engineer will seldom say that anything is impossible; rather, he tends to say that a phenomenon is so mathematically remote that it does not bear consideration. To a lawyer, a phenomenon is either possible or impossible.

The witness who emphatically states that a phenomenon is impossible leaves himself open to attack on his credibility if the opposing counsel can demonstrate that the proposition is not only possible but workable. Therefore, it is sometimes better to answer in terms of "I do not believe that it would be possible to..." even in terms of "I believe with the technology available today, one would be able to..."

11. The "please forget" question. Lawyers find that if they add the words "if you remember" to the beginning or the end of a question, very often the witness will not remember. There are times when a lawyer would prefer that the witness not remember. Sometimes the lawyer will add the phrase "if you remember" because it may suggest to the witness that he does not remember.

12. The "double negative" question. Occasionally, a lawyer will inadvertently phrase a question with two negatives, such as "You're not telling us that you didn't see the accident?" Obviously, such questions can create considerable confusion. In this instance, you would not answer with a simple "yes" or "no." One may state, "I didn't see the accident," or ask the attorney to rephrase the question in a more understandable form.

13. The "knowledge" question. The phrases "to your knowledge..." and "as far as you know..." present a special hazard when tacked onto a question. The witness may be induced to make an answer which implies something he does not intend. Consider the question: "To your knowledge, did the hospital consider these safety procedures before the incident?" The witness may not know whether such procedures were considered but is induced by the form of the question to respond with "Not to my knowledge." The answer suggests that such procedures were not considered. The witness should have answered, "I don't know."

14. The "Primrose Path" question. The Primrose Path is a tactic in which a witness is asked whether he agrees with carefully worded, very broad and oversimplified statements which, on the surface, appear undeniably true. The witness is led into voicing his agreement to one statement after another until he suddenly finds that he is trapped into a conclusion which he knows to be dead wrong.

The technique has been employed in different forms against engineers, physicians, and business and professional men.

Many lawyers feel that these are objectionable questions. Some lawyers may instruct witness not to answer these questions. The reason is that these questions really call for the witness to render a legal opinion as to the duty of a professional person. Note that such questions use the words "duty," "obligation," or "responsibility." The lawyer will insist that he is only setting "professional standards," but when he gets to court, he will read the question and answer to the jury and argue that the witness has violated a legal duty. Almost every Primrose Path question needs to be clarified.

Another reason the Primrose Path questions are objectionable is that they are almost always too broad to relate to the matter involved in the lawsuit.

15. The silent treatment. This is a subtle form of intimidation in which the lawyer, by silence, suggests that the witness should make another or a further answer. The lawyer may simply stare at the witness after the witness has answered a question. The witness may become uncomfortable or assume that his answer is incomplete; faced with an awkward silence many witnesses feel compelled to commence a defensive explanation of their answer. Some lawyers encourage the witness with the silent signals (expressions of interest, tilted head, raised eyebrows, hand extended with palm upward) while other lawyers may stare with a look of incredulous disbelief.

Do not be intimidated by these tactics. When you've answered a question, you should stop and wait for the next question. If the lawyer wants further information or a more detailed explanation, he will ask for it. If he employs the "silent treatment" you may ignore his tactics. If the lawyer sees that you're not afraid of silence he will move on to the next question.

16. The end of the line question. Lawyers should properly ask whether they have obtained all of the information a witness may have on a particular subject. For instance, an attorney may ask: "Is that all of the conversation which you had with the patient while she was under your care?" This is not a trick question; the attorney has the right to discover all of the admissions his client may have made in a conversation with the doctor. However, this presents a problem for the doctor inasmuch as he may not remember all of the details of the conversation with such particularity that he can relate them during his deposition. The doctor would like to leave the door open to the possibility that he will recall further details as time goes on. Under the circumstances, be as fair as you can. If you're certain that you have related all of the information you know, then say so. However, if you are uncertain, then it is permissible to answer stating: "I have told you about all of the conversation I can remember at this time."

17. The punch after the bell question. This is a tactic employed by counsel to persuade the witness to drop his guard before the end of the deposition. A lawyer may well say, "I think that's all of the questions I have; let me have a moment or two to review my notes." The lawyer may then study his notes for a few moments, close his notebook and give a weary look as if to say, "Well, we're through." The witness senses that the deposition has concluded and relaxes. Then, WHAM! the lawyer spends the next hour asking in rapid fire the toughest questions of the deposition. Remember, the deposition is not over until everyone leaves. Stay alert. ■

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To Contract or Not to Contract: That is the Question
Issues Raised by HMO and PPO Contracts

Susan E. Wells-Shapiro, Esq.

O'Connor, Cavanagh, Anderson, Westover,

Killingsworth & Beshears, P.A.

As any physician currently in practice knows, the health care system is changing rapidly. Due primarily to improvements in diagnostics and technology, and the increasing practice of defensive medicine, the cost of providing quality medical care is spiralling. According to the U.S. Department of Labor, since 1980, the average annual cost to businesses of providing medical benefits per employee has risen from $710 to $3,117. Health care costs are expected to increase an average of 22% this year. Employers are responding by increasingly offering alternative delivery systems, such as HMOs and PPOs (all types of alternative delivery systems are hereafter referred to individually as an "ADS"), to their employees and by providing financial incentives to encourage their employees to use them. More than 70% of Americans who obtain their health insurance through their employers are now participants in some kind of ADS. Nearly 650,000 Arizonans belong to some kind of ADS. As ADSs continue to attract an ever-increasing percentage of the population, physicians who do not participate in ADSs will increasingly find that they are losing patients to ADSs and that the number of their new patients is decreasing.

A physician considering a contract with an ADS is faced with a complex decision. Contracting with an ADS can have a significant impact upon a physician's practice--both in the way his practice is conducted and in financial terms. In addition, it is important to remember that the contracts that ADSs submit to physicians were drafted by the ADS' legal counsel, acting with the ADS' best interests in mind. Those interests generally include shifting liability to the physician and "managing" the manner in which the physician practices medicine so as to achieve the greatest possible cost savings. Obviously, those interests do not coincide with the interests of contracting physicians. Accordingly, a physician would be well advised to review those contracts with a critical eye, so that he can understand the new obligations imposed upon him by the contract, as well as the increased risk of participating in an ADS. In some cases, it may be adequate to obtain additional information that is not contained in the contract or clarification of an ambiguous term. In some cases, it may be appropriate to negotiate the terms of the contract so that they are more acceptable to the physician. In other cases, where negotiation is not possible, the physician may decline to participate in a particular ADS or may decide to nevertheless participate, but with a fuller understanding of his obligations and increased risk.

Standard of Care

One of the key factors a physician should consider in determining whether to contract with an ADS and in practicing under an ADS contract is whether the terms of the contract attempt to alter the physician's manner of practice in a way that is not compatible with good medical practice. An ADS contract does not alter the standard of care that a physician owes to his patient. Regardless of the trend towards ADS and the "managed care" brand of medicine promoted by them, a plaintiff's attorney will assert that his client was entitled to the best care medically possible at the time of treatment. As a result, use of medically advanced diagnostic tests and procedures is the advisable course of practice.

Accordingly, it is important to review the ADS contract to note which procedures require preauthorization, as well as the mechanism for obtaining preauthorization. Similarly, it is important to review the medical decision review and appeal procedure to confirm that it is both fair and practical. If in the physician's medical judgment a particular test or procedure is indicated, but the ADS refuses coverage, the physician should exhaust all efforts to aid the patient in seeking authorization for care, from

the ADS, or otherwise, and should document his patient files appropriately. If the preauthorization, medical decision review and appeal provisions are overly burdensome, they can increase a physician's risk of exposure to claims of professional liability, as well as his expenditure of time in connection with those processes.

In addition, a primary care physician should review the contractual provisions relating to preauthorization and financial disincentives of referrals to specialists, as well as the list of specialists who are participating physicians. If the preauthorization requirements or financial disincentives are burdensome or the list of participating specialists is deficient, either in number or in competence, the primary care physician could be increasing his exposure to risk.

Shifting Liability

Another key consideration is whether the ADS attempts to shift to the physician all of the liability for medical care, including liability arising out of the ADS' actions or inactions. Obviously, in attempting to limit the cost of medical care, an ADS will make decisions that may adversely impact the quality of the medical care received by a patient. With an indemnity provision, even if a physician vigorously challenges an ADS' decision with respect to a particular test or procedure, that physician would be liable to the patient for the adverse medical results. In contrast to the physician's liability for his own actions, his liability for the ADS' actions would probably not be covered by his professional liability insurance policy. Unless he requested that his professional liability insurance policy be modified to cover liability assumed by contract, or sought to obtain a new policy which includes such coverage, the physician would be obligated to pay any judgment rendered, as well as attorneys' fees incurred by him and the ADS.

Disclosure of Medical Records

The ADS contract should also be reviewed with respect to the requirement to disclose to the ADS information in patients' medical records. Although ADSs customarily obtain patients' consent to have their medical records released by physicians to the ADS, there can be no assurance that the ADS has done so. Therefore, the physician should obtain releases from his patients or copies of the releases provided by his patients to the ADS.

Participation in Peer Review Procedures

In reviewing an ADS contract, a physician should confirm whether he will be required to participate in the ADS' peer review procedures. Undertaking peer review for an ADS may subject a physician to exposure to both patients (for example, in connection with a decision to deny treatment) and participating physicians (for claims based on defamation, interference with business relationships and antitrust). Participation in peer review activities conducted by an ADS may not be protected by the immunity accorded to peer review activities conducted by hospitals. In addition, under most professional liability insurance policies, these claims would not be covered and the physician would be required to pay any judgment rendered against him, as well as his own attorneys' fees.

General Contract Issues

In addition to the considerations that relate specifically to health care contracts, physicians should review ADS contracts the same as they would any other contract. First, the contract should be complete and should not contain any blank spaces. If exhibits (for example, fee schedules) are referenced, they should be provided and reviewed. Second, the contract should contain all of the terms represented and promised by the ADS. The oral statements and commitments made by the ADS' marketing representative will be superseded by the terms of the contract and cannot be relied upon. Finally, and perhaps most importantly, the physician should understand the terms of the relationship with the ADS. If there are any ambiguities or the contract does not address a particular topic, the contract should be modified to clarify or address those points.

Financial Condition

Another concern, which is less legal and more practical, in connection with evaluating whether to contract with a particular ADS is the financial condition of that ADS. Although it appears that the ADS currently engaged in business in Arizona are improving their financial health (due, in part, to the bankruptcy or dissolution proceedings of the less financially able ADSs), it would be prudent to review an ADS' recent financial statement prior to signing any contract. Also, prompt payment of physician claims by an ADS will, in addition to improving the physician's cash flow, minimize his loss in the event that the ADS does become insolvent.

Most physicians who agree to contract with ADSs focus almost exclusively on the termination provisions of the contract. They figure that they will try it for a limited period and, if they are not satisfied with the terms of payment or the working relationship, they will terminate it. However, due to the increased exposure to risk which accompanies participation in an ADS, even during the limited period, physicians would be well advised to carefully review each proposed ADS contract. Only then can he fully understand its terms, appreciate the legal consequences of participation, and make an informed decision whether or not to participate. ■

Nationwide Hotline On STDs Expands Services

The National STD Hotline, a toll-free service covering the entire range of sexually transmitted diseases (STDs), has expanded its services beginning this month.

Increased funds will allow for: an increase in available telephone lines from five to eight; additional staffing; and a 25% increase in hours of operation. The Hotline is now open to calls from 8:00 a.m. to 11:00 p.m. (Eastern) Monday through Friday.

Sponsored by the U.S. Centers for Disease Control, The National STD Hotline (1-800-227-8922), has been handling calls from across the United States since 1979.

The expanded service, effective September 15, will be underwritten completely by federal funding. The Hotline will be operated under contract by the American Social Health Association (ASHA), a national non-profit organization dedicated to STD prevention and control.

In its first nine years of operation, over a third of the half million callers to the National STD Hotline have asked for information about genital herpes, which is estimated to afflict some 26 to 31 million Americans. Other STDs commonly asked about include gonorrhea, chlamydia, syphilis and non-specific urethritis. The Hotline's trained information specialists also provide referrals to public clinics that offer free testing and treatment. The service is toll-free and anonymous for callers from anywhere in the united States and its territories.

"The AIDS epidemic has appropriately absorbed much attention as a public health problem," says Peggy Clarke, executive director of ASHA. "But meanwhile other sexually transmitted diseases are on the rise. Because these parallel epidemics also place people at risk for AIDS, the prevention of all STDs is especially important today.

"ASHA will continue its role in promoting education about all sexually transmitted diseases and welcomes this opportunity to operate the expanded hotline for the Centers for Disease Control."

Dye Laser Removes Port wine Stains From Children

Until recently, birthmarks called port wine stains (for example, the birthmark on Soviet leader Gorbachev's forehead) were not considered treatable.

New developments in technology have now made laser treatment effective for removing port wine stains. Physicians at The University of Texas Southwestern Medical Center at Dallas are among those of the first five health-care institutions in the United States to experiment with a tunable dye argon laser to remove the birthmarks.

"Before this type of laser was developed, there was no acceptable treatment for port wine stains," said Lynne Roberts, M.D., assistant professor of dermatology and pediatrics at the medical school and co-director of dermatology at Children's Medical Center. "In addition to the medical implications, which include soft tissue deformity and vascular tumors, port wine stains are unsightly and often cause quite a psychological problem."

The dye laser can be tuned to the specific wavelength of light that will give the desired biological effect. According to Dr. Roberts, the 577-nm wavelength has been determined to be highly absorbed by blood vessels. The intense energy of the laser beam destroys the enlarged and excess blood vessels of the port wine stain while leaving surrounding, normal tissue unaffected.

Because the dye laser affects only the stained area, the risk of scarring, formerly between 50-60 percent with older types of laser treatment, is "virtually remote -- less than two percent," said Dr. Roberts.

Stain removal is especially beneficial for children because the unsightly appearance of port wine stains often causes psychological trauma for a child. Treatment at a young age can save a child many years of coping with low self-esteem.

Dr. Roberts is currently the only pediatric dermatologist in the North Texas area using dye laser technology to treat children with the birthmarks. Board certification in both dermatology and pediatrics has been especially important in her work with port wine stain removal in children.

Treatment with the dye laser involves tracing the stain with a continuous light beam. Because the process can be painful, sedation similar to the type used when an oral surgeon extracts teeth is given to children. The treatment itself is scheduled on an out-patient basis, as it usually takes no longer than one hour.

In the past two years, dermatologists at the medical center have treated 14 children and 40 adults with port wine stains. Dr. Roberts has performed dye laser surgery for an additional 70 patients with other vascular abnormalities including hemangiomas and telangiectasias (broken veins).

Port wine stains occur in approximately three out of every 10,000 births and affect Caucasians more often than blacks or Hispanics. At birth, the stains are flat with a pink or red coloration. They tend to darken and take on a raised or lumpy appearance throughout adolescence and adulthood. ■

Gleanings From the ArMA Past

John W. Foss, M.D., of Phoenix was president of ArMA in 1910. He was born in New Hampshire in 1862 of New England parentage. While the Foss family was of Norwegian origin, it was well represented in the Revolutionary War by seven men who bore the name of Foss. A graduate of Harvard Medical School, he arrived in Phoenix in 1899 via Colorado Springs.

One biographer noted, "He has been president of the Maricopa County and Arizona State Medical Societies, and public opinion places him in a leading position in the local profession."

He was an avid booster for the areas, "Its dry atmosphere, freedom from dust, purity of air, maximum sunshine, low altitude, gentle wind movement, freedom from snow and fogs, make it an ideal home for those who are in quest of health, comfort and wealth." This he stated as president of the board of trade. This must have been a precursor of the Chamber of Commerce.

The exalted description of the climate--in the Salt River Valley--bears little resemblance to the dust and smog laden atmosphere we now enjoy.

Dry Gulch Jake

Physicians in the News

Last April radiologist **William Horsley, M.D.**, medical staff member from Scottsdale Memorial Health Systems, Inc., participated in a medical mission to the

William Horsley, M.D.

Federated States of Micronesia, a small nation of islands located in the pacific just an hour north of Guam.

The 35-member team spent two weeks treating over 3,000 patients in this country ravaged by disease, desperately in need of quality health care. The team made "hut calls," traveling from island to island and hut to hut, treating everything from skin and parasitic infection and removing tumors from legs and stomachs to observing an occasional case of leprosy and many of Hepatitis Type B.

One of the main goals of the mission was to teach and educate, preaching sanitation and disease prevention, without destroying a culture that has existed on its own for centuries without "help."

Another trip to Micronesia is planned in the future. Interested physicians may call the Arizona Volunteer Medical Team at 481-4412, extension 2913.

Hunter Yost, M.D.

Tucson psychiatrist **Hunter Yost, M.D.**, recently set five Arizona State swimming records in National Masters Swimming competition. Four were accomplished at the National Masters Swimming Championships in Grand Forks, North Dakota, where he set records in the 200 and 400-meter freestyle events and in the 200 and 400-meter individual medley for the 35-39 age group. Competing against several former Olympic swimmers, he placed fifth in the 400-meter individual medley, sixth in the 200-meter individual medley and seventh in the 100-meter butterfly event.

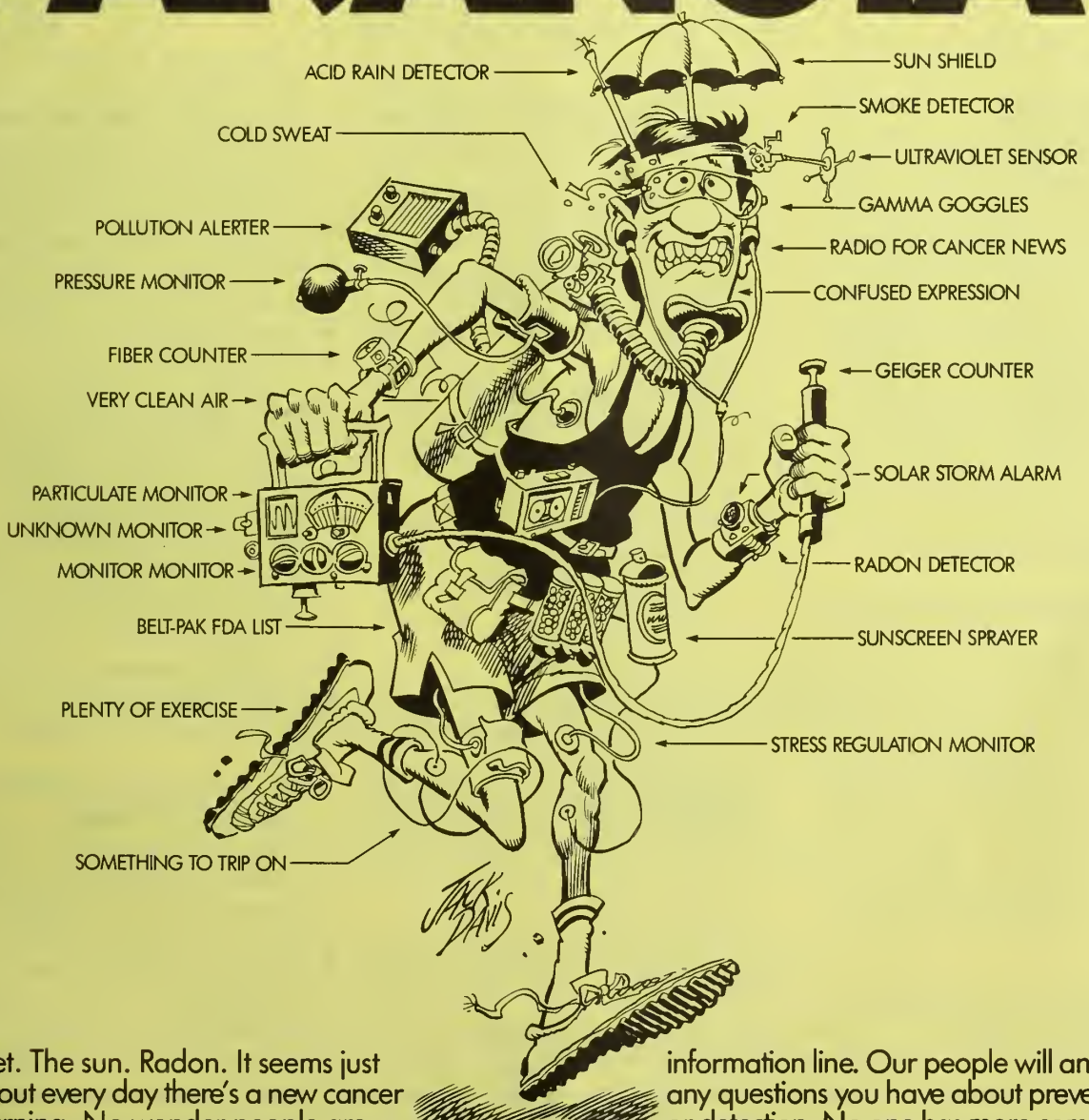
He set the other state record in the 800-meter freestyle event at a meet in Tucson last summer. Not only did he break state records at age 38, but these accomplishments were his own personal best times.

He said he has always enjoyed swimming plus he was blessed with natural ability. An avid swimmer since he was 9, he swam competitively in both high school and college. For the past 10 years he has been involved with the National Swimming Masters. One of the reasons he returned to competitive swimming was because he felt he had not yet reached his full potential.

During the summer when most competitive events are held, Dr. Yost swims five times a week for an hour and in the winter he swims three times weekly.

Dr. Yost has operated a private psychiatry practice focusing mainly on the family since 1982. ■

CANCER PARANOIA?



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HCPCS Coding

Introduction

In our last article, we discussed the proper use of CPT-4 coding, Level I of III in the CPT coding system. Today, we will discuss Levels II and III of CPT coding: Medicare's National and Local HCPCS (HCFA* Common Procedure Coding System). This article will explain how, when and why to use the HCPCS coding system in order for you to achieve optimum coding accuracy. Improved knowledge of the HCPCS coding system will also help increase practice revenue.

The Purpose of HCPCS Coding

In the early 1980s, HCFA introduced the HCPCS codes to be used specifically for Medicare/Medicaid charges and as supplement to the CPT-4 book. Durable medical equipment, injections, dental procedures, and orthotics help make up the more than 2,500 national HCPCS codes for supplies and services not contained in the CPT-4 book.

The Format of the National HCPCS Book, Level II

Through explanations and examples, the introduction of the HCPCS National Level II book addresses the distinct use of HCPCS codes. This introduction is most helpful when used together with that of the CPT-4 book. The supplies and services, identified by chapter, are as follows:

1. Transportation Services (Ambulance)
2. Chiropractic
3. Medical and Surgical Supplies
4. Miscellaneous and Experimental
5. Enteral and Parental Therapy
6. Dental Procedures
7. Durable Medical Equipment
8. Rehabilitative Services
9. Drugs Administered Other Than Oral Method
10. Chemotherapy Drugs
11. Orthotic Procedures
12. Prosthetic Procedures
13. Medical Services
14. Pathology and Laboratory
15. Temporary Codes
16. Diagnostic Radiology
17. Surgery
18. Vision Services
19. Hearing Services

In order to fully use the three levels of coding to your best advantage, it is important to understand the supplementary nature of HCPCS codes to those of CPT-4. And, as with the CPT-4 codes, you must avoid being "locked into" one set or category of HCPCS codes.

*Healthcare Financing Administration.

The Local HCPCS Codes, Level III

The local HCPCS codes are developed and administered by the Medicare carrier in each state. In Arizona, the Medicare carrier is Aetna. The local HCPCS codes represent certain specifications of supplies and services not contained in either the CPT-4 book or the HCPCS National Level II book. For example, the local HCPCS code WOOOO is for Cardiac Rehabilitative Services. However, the national HCPCS code closest to that service is H5299 (Rehabilitative Evaluation, Not Otherwise Classified). An appropriate CPT-4 code for that service does not exist. In contrast to the over 2,500 national HCPCS codes, there are fewer than 100 local HCPCS codes in Arizona.

What HCPCS Codes Look Like

Both the national and local HCPCS codes are easily identified by their alphanumeric combination. Unlike the all numeric CPT-4 codes, the HCPCS codes begin with a letter followed by numerals. 90050 is an example of a CPT-4 code, whereas A4550 is an example of an HCPCS code. The HCPCS and CPT-4 codes are all five digits in length.

When To Use the National and Local HCPCS Codes

Even though some private insurance carriers may recognize the national and local HCPCS codes, they were developed for Medicare and Medicaid charges only.

In searching for the most accurate HCPCS code you should always cross reference it with the CPT-4 book. By cross referencing, you are more likely to choose the most accurate code for your service. For example, assigning the CPT-4 code 99070 for an elastic bandage is correct if you are billing for non-Medicare/Medicaid services. However, for Medicare/Medicaid charges you should use the national HCPCS code A4460 because it better describes the supply. By using

the code that best describes your service, the charge is less likely to be questioned by Medicare/Medicaid.

Medicare prefers that, when appropriate, local HCPCS codes are used before the national HCPCS and CPT-4 codes. This is another step in making sure the most accurate code is submitted.

Reimbursement Based On the HCPCS Code

Medicare/Medicaid have established allowables for certain HCPCS codes which they cover. However, because Medicare/-Medicaid disallow some HCPCS codes, it is to your benefit to be aware of those codes. We should point out, however, that reimbursement is not guaranteed simply because an HCPCS code is submitted since each charge is unique to its situation. Information regarding allowables for all HCPCS codes can be obtained either from your Medicare profile or by contacting the local Medicare/Medicaid office.

Always use the most descriptive code available to ensure not only that you receive accurate reimbursement but that the charge is processed correctly. Using our example from above, Medicare may allow up to $15 for the CPT-4 code 99070 (Miscellaneous Supplies). However, if you use the national HCPCS code A4460 (Elastic Bandage) Medicare may only allow between $3 and $4. Although it appears to be substantially better to use code 99070 instead of A4460, Medicare will base its allowance in this case on the actual supply rather than on the code submitted. Thus, by submitting inaccurate codes you may inadvertently slow the processing of your claim.

Summary

When HCFA introduced HCPCS codes, physicians were expected to use them as a supplement to the CPT-4 codes. However, the purpose of HCPCS codes is still not widely understood due in part to the emphasis of CPT-4 coding within the medical community. By understanding the proper use of the HCPCS and CPT-4 codes you can achieve optimum coding accuracy while improving your practice revenue.

Claire Miller and Joan Miller are Presidents and Chief Financial Officer of SysteMedical Management, Inc., a medical practice management firm located in Mesa, Arizona. They can be reached at (602) 833-4855.

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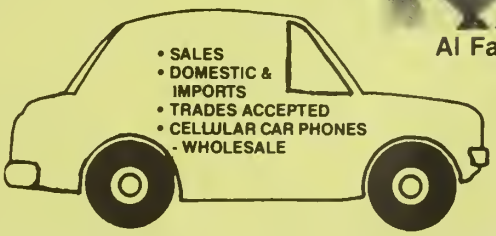

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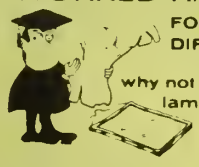

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Clinical Investigation

Orthostatic Hypotension, Catecholamines, and α-Adrenergic Receptors in Mitral Valve Prolapse

IRWIN J. SCHATZ, MD; SUBRAMANYAM RAMANATHAN, PhD; ROSIE VILLAGOMEZ, MS; *and* CHARLES MacLEAN, PhD, *Honolulu*

The reported association of mitral valve prolapse with autonomic dysfunction and neuroendocrine abnormalities is derived from studies of patients selected because of symptoms or specifically referred for investigation. To determine whether such associations occur in nonreferred and unselected women with mitral valve prolapse, we measured blood pressure, heart rate, and norepinephrine response to standing in 13 volunteers with mitral valve prolapse and in 11 control subjects. Platelet α-adrenergic receptor quantity and affinity on standing also were determined in all persons. No significant differences were found between the groups in any of these measurements. Although small subsets of women with mitral valve prolapse may indeed have associated neuroendocrine epiphenomena and autonomic dysfunction, it is probably incorrect to generalize these findings to the vast spectrum of those with mitral valve prolapse.

(Schatz IJ, Ramanathan S, Villagomez R, et al: Orthostatic hypotension, catecholamines, and α-adrenergic receptors in mitral valve prolapse. West J Med 1990 Jan; 152:37-40)

Ubiquity in medicine compels attention. Mitral valve prolapse (MVP) has received intense scrutiny, with a consequent generation of substantial quantities of published data; it is probable that some of these may have led to inappropriate conclusions. The concept that the presence of an audible midsystolic click or its echocardiographic correlates always indicates a disease state is an egregious example: thus, a malalignment of the mitral valve and left ventricle may be judged commonly to be associated with a number of important pathophysiologic disorders. For instance, a less-than-scrupulous reader may conclude that MVP has a strong relation with one or more of the following: orthostatic hypotension,[1] panic-anxiety attacks,[2] high α-adrenergic tone,[3,4] β-receptor hypersensitivity,[5] dysautonomia,[6] abnormal catecholamine responses,[7,8] and autonomic dysfunction.[9,10] In fact, these careful studies found abnormalities in MVP patients who were usually symptomatic and who had been specifically referred to cardiac centers for investigation and care. Such selected subjects clearly represent only one part of a vast spectrum of people in whom this anatomic variant exists.

The purpose of our investigation was to determine if postural hypotension, an abnormal heart rate response to standing, excessively elevated catecholamine levels, and altered α-adrenergic receptor quantity and affinity when upright were present to a substantially greater degree in persons with asymptomatic MVP than in controls. Our goal was to study a group of patients with MVP who would reflect, as much as was possible, the actual distribution of that variant in the general population.

Study Population

To obtain an unbiased sample of women with MVP, a one-time notice was sent to medical students, department personnel, and faculty cardiologists asking for volunteers both with and without known, untreated MVP. Exclusions included male sex, age younger than 18 or older than 50, and the use of β-adrenergic blocking or oral contraceptive drugs.

A total of 24 persons were recruited, 13 with MVP and 11 without. Mitral valve prolapse was confirmed on the basis of the unmistakable presence of one or more midsystolic clicks and the typical findings of MVP on the long axis parasternal view of a two-dimensional echocardiographic study. Neither systolic clicks nor late systolic murmurs were heard in the control subjects; a two-dimensional echocardiogram was normal in each. None of the subjects had a chronic illness, took neuroactive medications, smoked, or had consumed caffeine for at least 12 hours before the study.

Protocol

Each person had nothing to eat or drink after midnight; tests were scheduled at 7:30 AM. A heparin-lock needle was inserted into a forearm vein and, to diminish the effect of psychological stress, the subject then rested in a darkened room for 30 minutes. While in this resting supine basal state, the heart rate and forearm blood pressure (BP) were recorded; a venous specimen was also taken to measure the plasma norepinephrine level. Each person then stood quietly for three to five minutes during which the pulse and BP were again recorded and a blood specimen removed for measuring both a plasma norepinephrine level and platelet α-receptor

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ABBREVIATIONS USED IN TEXT

BP = blood pressure
EDTA = ethylenediaminetetraacetate
MVP = mitral valve prolapse

quantity and affinity. A total of 110 ml of blood was removed.

Catecholamines were measured by the standard method of Peuler and Johnson.[11] Laboratory technicians did not know whether plasma specimens came from persons with MVP or from control subjects.

Changes from supine to standing were compared in patients with MVP and in control subjects by the method of analysis of variance. Blood pressures, heart rates, and norepinephrine levels were adjusted for both age and basal (supine) level.[12]

Studies on the specific binding of [^{3}H]yohimbine indicate that the adrenergic receptors on human platelets are exclusively of the α_2 subtype. The specific binding of this ligand to platelet α_2-adrenergic receptors has been suggested to be altered in a variety of disease states.[13] Therefore, the specific binding of yohimbine to platelet membranes was measured in control subjects and in patients with MVP.

Platelet membrane was prepared from the blood specimens as described by Newman and co-workers.[14] About 100 ml of whole blood was collected with an anticoagulant (3.2% citric acid). The blood specimen was centrifuged at 380*g* for ten minutes at 25°C. The resulting platelet-rich plasma was collected and centrifuged again at 16,000*g* for ten minutes at 4°C to sediment the platelets. The pellet was washed three times in cold buffer (0.05 mol per liter tris hydrochloride, 0.15 mol per liter sodium chloride, and 0.02 mol per liter ethylenediaminetetraacetate [EDTA], pH 7.35) and centrifuged again at 16,000*g* for ten minutes at 4°C. Following freezing under liquid nitrogen, then thawing at room temperature, the washed pellet was lysed by homogenization (30 strokes) in 1 ml lysing buffer (0.005 mol per liter tris hydrochloride, 0.005 mol per liter EDTA, pH 7.5) with a motor-driven Teflon-tipped pestle. The final pellet was resuspended in lysing buffer (1 mg per ml) and used immediately. The platelet membrane protein was assayed using the method of Lowry and associates and bovine serum albumin as the standard.[15]

The total yohimbine binding was measured in a final volume of 150 μl containing incubation buffer (0.05 mol per liter tris hydrochloride, 0.005 mol per liter EDTA, pH 7.5), varying concentrations of yohimbine (0.05 to 25 mmol per liter), and freshly prepared platelet membranes. Reactions were initiated by adding membranes and incubating for 20 minutes at 32.5°C. Incubations were terminated by adding 4.0 ml cold incubation buffer. The contents of the tubes were rapidly filtered through Whatman GF/C filters and washed with two 4.0-ml aliquots of incubation buffer. The filters were then dried at 75°C to 90°C and counted in a liquid scintillation counter. Specific binding was defined as yohimbine displaceable by 10^{-5} mol per liter unlabeled yohimbine. All experiments were run in duplicate. Estimates of the maximum number of binding sites (B_{max}) and the apparent dissociation constants (K_d) were determined by Scatchard analysis.[16] In the Scatchard plot the amount of ligand bound is plotted against the ratio of the bound to the free ligand, the B_{max} is the x-intercept, and the K_d is the negative of 1/slope.

Results

There were 13 women with mitral valve prolapse (average age 29.6 years; range, 18 to 40) and 11 control subjects (average age 32.5 years; range, 19 to 49). One person with MVP reported occasional dizziness when upright; otherwise, all were without symptoms.

Standing induced a trivial decline in the systolic blood pressure in both groups; the normal, physiologic increase in the heart rate when upright was not different in MVP patients when compared with controls. Similarly, the elevation in plasma norepinephrine levels, which normally occurs on standing, was not significantly different between the two groups (Table 1).

The 95% confidence limit on differences between persons with mitral valve prolapse and control subjects indicated that the probability that we missed a physiologically important difference (type 2 error) because of an insufficient number of study subjects is negligible (Table 2). Moreover, no differences between the control subjects and the patients with MVP were detected in the measurement of the total number of α-adrenergic receptors (B_{max}) and the dissociation constant reflecting α-adrenergic receptor affinity (K_d) (Table 3).

TABLE 1.—*Orthostatic Changes in Systolic Blood Pressure (BP), Heart Rate, and Plasma Norepinephrine Level**

	Subjects			
	Control, n=11		MVP, n=15†	
Variable	Average	SD	Average	SD
Supine systolic BP, mm of mercury	103.0	8.9	101.4	9.5
Standing systolic BP, mm of mercury	101.6	10.3	96.6	8.6
Δ in BP	−1.4	8.0	−4.8	8.6
Supine heart rate, beats/min	66.2	9.1	66.8	7.3
Standing heart rate, beats/min	86.8	10.8	87.1	7.2
Δ in heart rate	+20.6	9.6	+21.3	5.9
Supine plasma norepinephrine, nmol/liter	1.276	0.549	1.111	0.342
Standing plasma norepinephrine, nmol/liter	2.736	1.205	2.849	1.022
Δ in plasma norepinephrine	+1.460	1.205	+1.738	0.833

MVP=mitral valve prolapse, SD=standard deviation

*Not adjusted for age and the mean values of the corresponding variable.
†Two subjects were studied twice on 2 separate occasions.

Discussion

In sum, the present data provide no positive evidence of a difference between control subjects and women with mitral valve prolapse in any of the measurements shown in Tables 2 and 3. Although the problem of demonstrating the negative proposition that no differences exist is always more difficult, these data do provide a maximum plausible limit to the variation. For the changes in blood pressure and heart rate, the extreme 95% confidence limits on results between controls and MVP subjects shown in Tables 2 and 3 are such that even if the actual differences were to lie at these limits, they would be physiologically unimportant. For norepinephrine, it is statistically possible, but highly unlikely, that the maximum difference between patients with MVP and controls was 0.721 nmol per liter—about 40%. Thus, although our best estimate is that the variation is much smaller, an increase in norepinephrine cannot be ruled out as a distinguishing factor between controls and MVP subjects.

Thus, we have found no significant differences between our control subjects and those with the clinical and echocardiographic signs of MVP in heart rate, blood pressure, and catecholamine response to standing and in the quantity and affinity of platelet α-adrenergic receptors. Our selection of patients was based solely on the presence or absence of the signs of MVP and not on referral for symptoms or investigation.

Men were finally excluded from the study because our initial request elicited only women volunteers; we subsequently decided to exclude men when only one man volunteered as a control subject. We thought it would be prudent to avoid the potential of sex-determined biologic differences. Whether canvassing for volunteer women working in a hospital or medical school environment closely simulates the universe of MVP is arguable, but it is probably more representative of the general distribution of this disorder in society than would be those patients selected or referred specifically. The data from this group therefore suggest that the vast majority of patients with this anatomic deviation have no abnormal neuroendocrine process.[17]

A number of studies have provided conflicting evidence about the presence or absence of hemodynamic or autonomic nervous system abnormalities in patients with MVP. Such investigations are usually based on an examination of those who have been referred because of specific complaints or for investigation for a particular reason. For instance, Santos and colleagues examined 86 consecutive patients with echocardiographic criteria for MVP and found that 12 of them had substantial orthostatic hypotension.[1] The assumption is that they were referred to the echocardiography laboratory for a specific reason. Venkatesh and co-workers concluded that patients with anxiety neurosis and panic disorders had a higher incidence of MVP because they studied 112 patients with anxiety neurosis from whom 20 were selected for careful study of cardiac findings.[2] Of these, eight were found to have echocardiographic signs of MVP. Their original group of 112 patients had been observed carefully in the psychiatric clinic at the University of Iowa Medical Center. Davies and associates, in an elegant study, found physiologic and pharmacologic β-adrenergic hypersensitivity in nine symptomatic women.[5] Coghlan and co-workers chose 44 patients with MVP from a large population referred to the University of Alabama Medical Center; a number of different signs of autonomic dysfunction were found in this group.[6] Pasternac and colleagues showed that there were increased levels of plasma catecholamines in 15 MVP patients selected for study.[7] Boudoulas and associates investigated 20 symptomatic MVP patients and showed a greater than normal increase in catecholamines with exercise and an increased number of premature ventricular complexes in their patients.[8] Similarly, Gaffney and colleagues concluded that there were hemodynamic abnormalities in 23 women with symptoms "commonly associated with MVP."[9]

Contrary data were provided by Chesler and coinvestigators: they studied 11 consecutive MVP patients, 6 of whom were symptomatic. Although it is unclear whether all 11 had been referred for investigation, there was no evidence of autonomic dysfunction or of neurosis in this group.[18] The presence or absence of specific symptoms could not be correlated with the diagnosis of MVP made by echocardiography, according to a study by Retchin and co-workers.[19] This judgment was made on the basis of a retrospective assessment of medical records, a subsequent correlation with echocardiographic findings, and then telephone interviews of those patients found to be symptomatic.

What are we to make of these disparate results?[17] Clearly, comparisons derived from such studies are hazardous because the characteristics of MVP subjects differ substantially and the selection criteria for investigation of patients vary. Furthermore, serious methodologic problems exist when applying identical experimental designs to patients with vague,

TABLE 2.—*Statistical Evaluation of Changes on Standing for Patients With Mitral Valve Prolapse (MVP) and Controls**

Variable	*Decline in Systolic Blood Pressure, mm of mercury*	*Increase in Heart Rate, beats/min*	*Increase in Norepinephrine Level, nmol/liter*
Overall sample mean, n=34	3.2	20.4	1.601
Standard deviation	±8.4	± 8.0	0.715
MVP mean	3.9	20.1	1.720
Control mean	2.4	20.8	1.477
Difference between MVP and control means	+1.5	− 0.7	+0.242
	NS	NS	NS
Extreme 95% confidence limit on difference	+7.6	+ 4.7	+0.721

NS=not statistically significant

*All data are adjusted for age and for the mean values of the corresponding variable.

TABLE 3.—*Platelet α-Receptor Affinity and Quantity Measurements in Patients With Mitral Valve Prolapse (MVP) and in Control Subjects**

Variable	K_d, *mmol/liter*†	B_{max}, *fmol/mg protein*‡
Overall sample mean	5.1	298.0
Standard deviation	±3.0	±135.0
MVP mean	5.6	272.0
Control mean	5.1	316.0
Difference between MVP and control means	±0.5	− 44.0
	NS	NS
Extreme 95% confidence limit on difference	+2.6	−135.0

NS=not statistically significant

*Adjusted for age and mean value of the corresponding variable.
†K_d refers to the dissociation constant reflecting α-adrenergic receptor affinity.
‡B_{max} is the maximum number of binding sites for receptors.

general, and common complaints. The claims generated from each of these studies, therefore, are pertinent only to those patients within the study group; the presence or absence of specific abnormalities in hemodynamics, catecholamines, and an increased incidence of panic or anxiety attacks is entirely dependent on the nature of the individual group studied.

Unfortunately, a commonly held assumption is that mitral valve prolapse is a disease process often associated with serious neuroendocrine abnormalities. This is because the conclusions derived from specific investigations of patients referred or selected are mistakenly generalized to the entire universe of MVP subjects. Boudoulas and associates rightly emphasize the distinction between MVP and what they term "mitral valve prolapse syndrome," which connotes those MVP patients who also show varying degrees of autonomic disturbance.[8] The vast majority of those with MVP clearly do not fall into this latter category.

Mitral valve prolapse is likely an anatomic disorder that only rarely results in serious consequences for patients. Most people with this variant lead a normal life and do not have any important physiologic abnormalities.[17]

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The Effect of Chromium Picolinate on Serum Cholesterol and Apolipoprotein Fractions in Human Subjects

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Chromium has been implicated as a cofactor in the maintenance of normal lipid and carbohydrate metabolism. A deficiency of chromium results from diets low in biologically available chromium. Picolinic acid, a metabolite of tryptophan, forms stable complexes with transitional metal ions, which results in an improved bioavailability of the metal ion chromium. To determine whether or not chromium picolinate is effective in humans, 28 volunteer subjects were given either chromium tripicolinate (3.8 μmol [200 μg] chromium) or a placebo daily for 42 days in a double-blind crossover study. A 14-day period off capsules was used between treatments. Levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, and apolipoprotein B, the principal protein of the LDL fraction, decreased significantly while the subjects were ingesting chromium picolinate. The concentration of apolipoprotein A-I, the principal protein of the high-density lipoprotein (HDL) fraction, increased substantially during treatment with chromium picolinate. The HDL-cholesterol level was elevated slightly but not significantly during ingestion of chromium picolinate. Only apolipoprotein B, of the variables measured, was altered significantly during supplementation with the placebo. These observations show that chromium picolinate is efficacious in lowering blood lipids in humans.

(Press RI, Geller J, Evans GW: The effect of chromium picolinate on serum cholesterol and apolipoprotein fractions in human subjects. West J Med 1990 Jan; 152:41-45)

Heart disease is one of the leading causes of death in the world today, and among the factors that lead to heart disease is hypercholesterolemia.[1-3] Several factors have been implicated as the cause of hypercholesterolemia, including diet.[4] Diet is responsible for elevated cholesterol levels through both excesses and deficiencies of certain nutrients. Among the possible deficiencies in the diet are some trace minerals, and one that has been implicated is chromium.[5-9]

Early experiments showed that elevated serum cholesterol levels and aortic plaques occurred when diets deficient in chromium were fed to rats. The lipid abnormalities were not present in rats given supplemental chromium chloride.[5] When atherosclerotic plaques were induced in rabbits by a high-cholesterol diet, regression of the plaques was observed when the animals were injected with potassium chromate.[6] In humans, Schroeder and co-workers first discovered that aortas of persons who died of heart disease contained substantially less chromium than aortas from healthy accident victims.[7] Moreover, in a carefully conducted study, Newman and associates showed that patients with coronary artery disease had lower serum chromium concentrations than subjects with normal arteries.[8] Later, Simonoff and colleagues obtained identical results.[9] Most striking is the fact that both Newman and Simonoff and co-workers noted that coronary artery disease was most prevalent in persons with plasma chromium levels of less than 0.006 μg per liter.

Chromium deficiency occurs when dietary intake fails to keep pace with loss.[10] An inability to obtain enough chromium from the diet occurs for two basic reasons, the obvious lack of metal in the diet and the less obvious availability of the chromium that is present in the diet. The 1980 National Research Council, National Academy of Sciences, recommendation for a safe and adequate intake for chromium is 50 to 200 μg a day.[11] Some studies conclude that the standard North American diet contains less than 50 μg per day chromium.[12,13] Most processed foods contain decreased amounts of chromium.[11,13] In addition, serum chromium levels decrease with age, and the amount of chromium excretion increases with infection, pregnancy, high glucose intake, and stress.[14-18]

Due to the ever-present competing ions such as copper, iron, manganese, and zinc, as well as the tendency for hydration and possibly other factors, the availability of chromium from the diet may be as much a problem as quantity. Several studies have provided evidence that an adequate absorption of chromium occurs only when the metal is associated with a specific organic molecule synthesized in kidney and certain yeast.[10,19,20] Because these food items are not staples of modern diets, many investigators have attempted to isolate and identify a chelator that will improve the utilization of chromium. Picolinic acid is an effective metal chelator synthesized from tryptophan in both mammalian kidney cells[21] and brewer's yeast (H. Peppler, PhD, written communication, April 1987).[22] In addition, picolinic acid has been iden-

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ABBREVIATIONS USED IN TEXT
HDL = high-density lipoprotein
LDL = low-density lipoprotein

tified in both intestinal cells and human milk,[23,24] and complexes of zinc and picolinate are used much more efficiently than other forms of zinc.[21,25] Thus, picolinic acid may be a naturally produced ligand that facilitates the absorption and transport of ions in children and adults. Because chromium readily forms stable complexes with picolinic acid, this study was designed to test the effectiveness of chromium picolinate in humans.

Subjects and Methods

Subjects for the study were obtained after screening volunteers from among employees of Mercy Hospital and Medical Center, San Diego, California, and friends and relatives. A total of 32 volunteers aged 25 to 80 years with total cholesterol levels of 5.7 to 8.3 mmol per liter (220 to 320 mg per dl) were initially chosen. No subject had a history of hypothyroid disease, renal failure, liver disease, diabetes mellitus, known familial lipid disorder, alcohol or drug abuse, bleeding disorders, multiple allergies, or any other serious medical illness, and none were pregnant at the outset. None of the subjects were using β-blockers, thiazide diuretics, steroids, chromium supplements, or any investigational drugs. The volunteers were requested not to alter their dietary or exercise habits during the course of the study. Informed consent was obtained as specified by the Mercy Hospital Institutional Review Committee, and the subjects were paid a stipend for their participation.

Chromium tripicolinate, herein referred to as chromium picolinate, was synthesized by first dissolving 2.66 grams chromic chloride in 25 ml warm (60°C) deionized water. Thereafter, 3.69 grams picolinic acid (Sigma Chemical, St Louis) was added, and the contents were stirred with gentle heating until the solution turned purple and crystals began to form. The solution was then left standing at 4°C overnight. The supernatant was then discarded, and the crystals were air-dried at room temperature. An analysis of the crystals indicated that the complex consisted of 3 mol picolinate per 1 mol Cr^{+3}, with a molecular weight of 418.

For the double-blind, crossover study, subjects were divided randomly into two treatment groups by a nonparticipant. During each half of the study, participants ingested one gelatin capsule per day that contained either chromium picolinate or a placebo. The chromium picolinate supplement contained 1.6 mg chromium tripicolinate (200 μg Cr^{+3}) mixed with 5 mg calcium phosphate. The placebo contained only 5 mg calcium phosphate. The study consisted of two 42-day periods with a 14-day period off capsules between treatments. Compliance was monitored by a capsule count.*

At the beginning, after three weeks, and at the end of each period, heart rate, blood pressure, weight, and temperature were measured and a fasting blood specimen was drawn. The serum variables measured included total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, apolipoprotein A-I, and apolipoprotein B. Serum concentrations of cholesterol and triglycerides were determined with an Olympus 500 Automated Colormetric System (Olympus Instrument Co, Los Angeles). The HDL-cholesterol level was assayed with an enzyme heparin-manganese chloride precipitation method.[26] The LDL-cholesterol value was estimated by the method of Friedewald and co-workers.[27] Concentrations of apolipoprotein A-I and apolipoprotein B in serum were assayed with a nephelometric immunoassay[28] using a Boehringer laser kit.

For statistical analysis, the values obtained at the beginning and at the end of each 42-day period were used. Because each subject served as his or her own control, paired t tests were used to identify statistically significant differences between mean values of changes and differences in changes. Student's t test and P values were determined with the program "WormStat."*

Results

At the completion of the study, 28 of the original participants remained. Two subjects had moved, one became pregnant, and one, a 51-year-old woman, started menopause and began having "hot flashes."

The results obtained after analyzing the serum cholesterol and serum apolipoprotein fractions are shown in Figures 1 through 4. As shown in Figures 1 through 3, total cholesterol, LDL-cholesterol, and apolipoprotein B levels were all significantly decreased ($P=.007$, $P=.015$, and $P=.003$, respectively) during the first six-week period in subjects who began the study with the chromium picolinate supplement. The effect of chromium picolinate apparently persisted after the supplement was discontinued because the levels of each of those three variables after 14 weeks were lower than the initial levels (Figures 1 through 3). No significant alterations ($P>.05$) were observed in any of these variables during the last six-week period when the subjects were ingesting the placebo.

No significant change ($P>.05$) was observed in either serum total cholesterol or LDL-cholesterol levels during the first six-week period among the subjects who began the study with the placebo supplement. The levels of both total cholesterol and LDL-cholesterol, however, decreased significantly

*Research was coordinated by Elizabeth Maiwurm, RN.

*Statistical analysis was done by Jim Koziol, PhD, Scripps Clinic and Research Foundation, La Jolla, California.

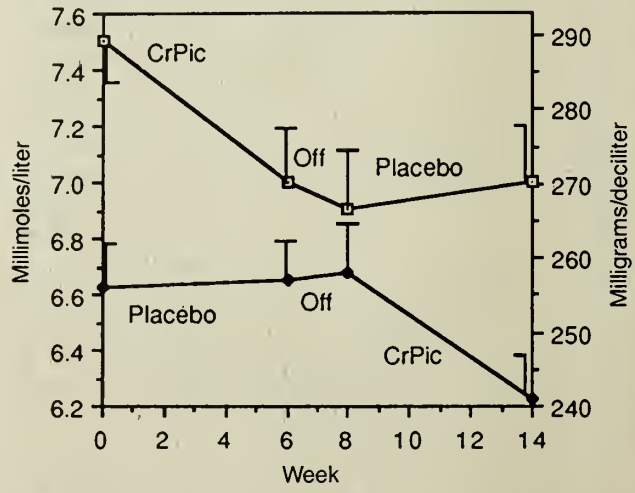

Figure 1.—Serum total cholesterol levels are shown in subjects supplemented alternately with chromium picolinate (CrPic) and a placebo for 6 weeks. The vertical lines depict the standard error of the mean.

($P=.009$ and $P=.003$, respectively) during the final 42 days while these subjects were ingesting the chromium picolinate supplement (Figures 1 and 2). In the group that began the study with the placebo, apolipoprotein B levels increased slightly but not significantly ($P=.058$) during the first eight weeks and then decreased, but not significantly ($P=.072$), after supplementation with chromium picolinate (Figure 3). The apolipoprotein A-I level was significantly elevated ($P=.047$) during the first six-week period in the subjects who started the study with the chromium picolinate supplement. No significant change ($P>.05$) was observed during the final 42 days. Apolipoprotein A-I levels in the placebo-first group increased, but not significantly ($P=.165$), during the first six weeks and then decreased during the off-capsule period. During the chromium picolinate supplementation period, apolipoprotein A-I levels were increased significantly ($P=.007$) in these subjects (Figure 4).

The consolidated results of the study are listed in Table 1. When the results from the 28 subjects were combined, significant ($P<.001$) reductions occurred with both total cholesterol and LDL-cholesterol concentrations during the 42-day period that chromium picolinate was ingested. The total cholesterol concentration decreased 7% from 7.1 to 6.6 mmol per liter (276 to 256 mg per dl) while LDL-cholesterol levels decreased 10.5% from 5.7 to 5.1 mmol per liter (200 to 178 mg per dl) during treatment with chromium picolinate. Of the final 28 subjects, 22 had lower total cholesterol values, 2 had no changes, and the remaining 4 had cholesterol concentrations elevated less than 0.1 mmol per liter (5 mg per dl). With LDL-cholesterol, 20 subjects had decreased concentrations, 3 had no changes, and the others had slightly elevated concentrations of LDL-cholesterol. The concentration of serum HDL-cholesterol increased slightly but not significantly ($P>.05$) during the period the subjects were ingesting chromium picolinate.

While subjects were ingesting the placebo, slight but statistically insignificant ($P>.05$) elevations occurred in the serum levels of both total cholesterol and LDL-cholesterol.

When the volunteers were treated with chromium picolinate, the concentration of serum apolipoprotein B, the principal protein of the LDL-cholesterol fraction, was decreased significantly ($P=.001$). An analysis of the values obtained from all 28 subjects showed a reduction of 16% from 155 to 130 mg per dl. The principal protein of the HDL-cholesterol fraction, apolipoprotein A-I, was significantly elevated ($P=.003$) in the serum of subjects ingesting chromium picolinate.

During the period the subjects ingested the placebo, apolipoprotein B was elevated significantly ($P<.05$). A slight but not significant ($P>.05$) elevation in apolipoprotein A-I was also observed while the subjects were supplemented with the placebo. No significant changes occurred in serum triglyceride levels, weight, blood pressure, temperature, or heart rate with either chromium picolinate or placebo.

Despite the fact that the supplements were distributed randomly, the concentration of each of the lipid variables was consistently lower in the subjects at the start of the placebo supplementation period. By coincidence, the 14 subjects who started the trial with the placebo had serum lipid levels considerably lower than the 14 who started with chromium picolinate. Thus, because the mean levels of 14 subjects were initially lower, coupled with the fact that the other 14 started with lower lipid levels resulting from successful

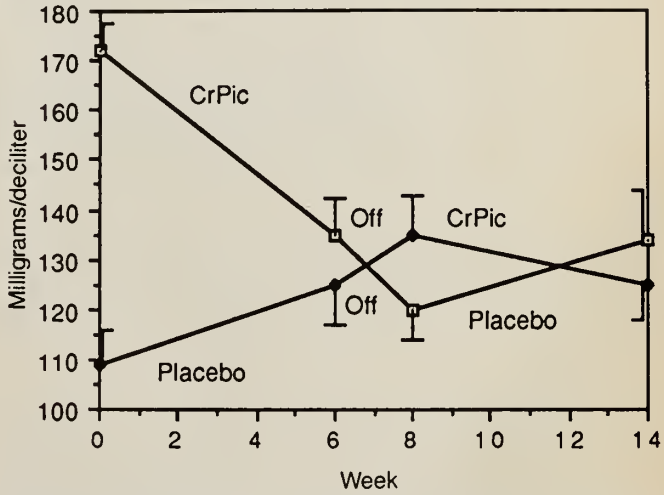

Figure 3.—Serum levels of apolipoprotein B are shown in subjects supplemented alternately with chromium picolinate (CrPic) and a placebo for 6 weeks. The vertical lines depict the standard error of the mean.

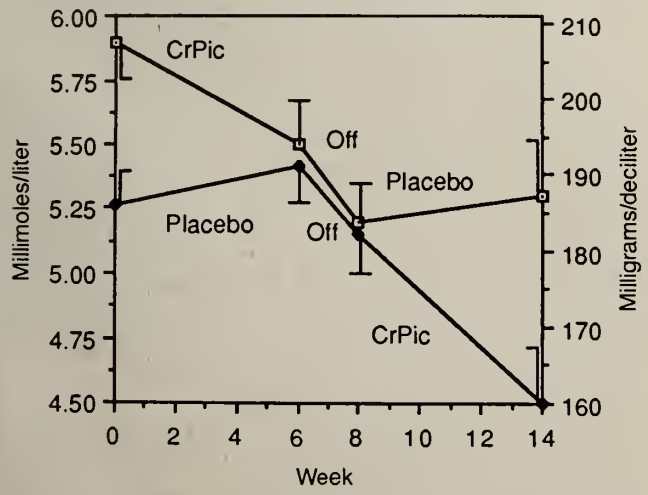

Figure 2.—Serum low-density lipoprotein cholesterol levels are shown in subjects supplemented alternately with chromium picolinate (CrPic) and a placebo for 6 weeks. The vertical lines depict the standard error of the mean.

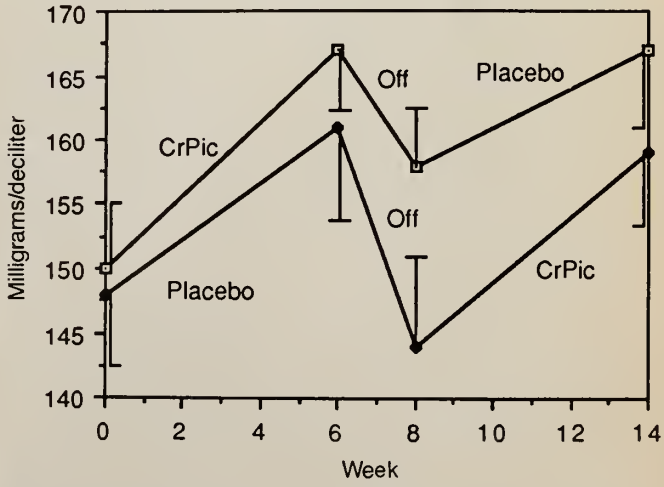

Figure 4.—Serum levels of apolipoprotein A-I are shown in subjects supplemented alternately with chromium picolinate (CrPic) and a placebo for 6 weeks. The vertical lines depict the standard error of the mean.

TABLE 1.—*Serum Lipid Values After Supplementation With Chromium Picolinate and Placebo**

	Treatment					
	Chromium Picolinate			Placebo		
Serum Fraction	Initial	Final	Change (P)	Initial	Final	Change (P)
Cholesterol						
Total, mmol/liter	7.1±1.0	6.6±1.0	− 0.5	6.8±0.9	6.8±1.0	+ 0.1
mg/dl	276±40	256±41	−19 (.0003)	262±34	265±38	+ 3 (.282)
LDL, mmol/liter	5.7±1.1	5.0±1.0	− 0.6	5.2±0.9	5.3±0.8	+ 0.1
mg/dl	200±39	178±35	−21 (.0003)	184±31	188±30	+ 4 (.106)
HDL, mmol/liter	1.3±0.4	1.4±0.4	+ 0.1	1.4±0.3	1.4±0.4	+ 0
mg/dl	52±16	55±17	+ 3 (.118)	53±13	53±17	+ 0.7 (.369)
Apolipoproteins						
Apo A, mg/dl	147±28	163±31	+16 (.003)	153±26	164±40	+11 (.077)
Apo B, mg/dl	155±50	130±45	−25 (.001)	115±32	129±36	+14 (.023)
Triglycerides						
mmol/liter	1.9±0.7	1.9±0.9	− 0	1.9±0.7	2.0±1.0	+ 0.1
mg/dl	168±65	167±76	− 1 (.246)	165±65	175±88	+10 (.151)

HDL=high-density lipoprotein, LDL=low-density lipoprotein

*The values listed were obtained by calculating the mean plus or minus the standard deviation for all subjects before and after the intake of chromium picolinate or placebo regardless of the order of supplementation. Thus, the values represent a composite mean±SD for all 28 subjects completing the study. Statistical significance of the changes was determined from the paired values for each person as described in the text.

and persistent treatment effects with chromium picolinate, the numeric means listed in Table 1 are less at the start of treatment with the placebo. As shown in Figures 1 through 4, regardless of the starting level, treatment with chromium picolinate produced significant changes.

Discussion

The results obtained in this study show that chromium picolinate may be an effective agent for treating serum lipid disorders. In a related study, we observed significant decreases in the levels of both fasting glucose and glycosylated hemoglobin in 11 persons with diabetes mellitus.[29] Thus, chromium picolinate is a biologically active form of chromium. Some published studies have shown no beneficial effects from chromium supplementation. Anderson has suggested that in those studies, the subjects may have had adequate chromium nutriture, which would explain the lack of effect.[30] To date, however, studies involving chromium have been confined to supplementation with chromium salts, high chromium yeast, or other organic forms of chromium. Although an adequate chromium status of the body might preclude effective treatment with chromium supplements, the bioavailability of the chromium must also be considered as a contributing factor.

Because several investigations have implicated chromium as a regulatory component in lipid and carbohydrate metabolism,[5-10] we assume that the chromium ion is the active factor while picolinic acid serves as the chelator to improve bioavailability.[21] Because the experimental design precluded obtaining direct evidence that chromium is the active ingredient of the complex, however, one cannot dismiss the possibility that the entire chromium picolinate complex may be involved. Also, because picolinic acid is an isomer of nicotinic acid, which is used in high doses to lower blood lipids,[31] there is a possibility that the picolinic acid caused the changes observed. This is unlikely because the daily intake of picolinic acid in the supplement was less than 2 mg while several hundred times that dose of nicotinic acid is required to treat hypercholesterolemia.

In this trial study, four of the six serum lipid variables measured were altered during the period the subjects ingested chromium picolinate. Levels of total cholesterol, LDL cholesterol, and the related transport protein apolipoprotein B were decreased, but the values of the apolipoprotein A-I, the HDL-cholesterol-related protein, were elevated when the supplement contained chromium picolinate. Because each of these variables is related either directly or inversely to the development of coronary artery disease, chromium picolinate is an excellent agent to consider in the treatment and prevention of hyperlipidemia.

The total cholesterol level is a treatable risk factor for coronary artery disease.[1-3] During the 7.4-year Lipid Research Clinics Coronary Primary Prevention Trial, an overall reduction of cholesterol levels of 8.5% was associated with a 19% decrease in the incidence of coronary artery disease. Furthermore, the initial stages of atherosclerosis are directly related to the level of LDL cholesterol.[32] Both of these lipid fractions were decreased significantly after only 42 days of supplementation with chromium picolinate. Total cholesterol levels were reduced 7%, and LDL-cholesterol levels were decreased 10% with this treatment.

Several recent studies show that specific lipoproteins are associated with heart disease.[33-40] In patients with documented coronary artery disease, elevated levels of apolipoprotein B coupled with reduced levels of apolipoprotein A-I were observed. During our study, supplementation with chromium picolinate resulted in a substantial elevation of apolipoprotein A-I levels and a notable reduction of apolipo-

protein B levels. Some investigators have suggested that levels of apolipoprotein A-I and apolipoprotein B are better predicters of coronary artery disease than levels of total, LDL, or HDL cholesterol.[39,40]

Because of the strong correlation between heart disease and serum lipids, the question today is not whether or not to treat these disorders but how and in whom. Although treatment with chromium picolinate did not return all the lipid moieties to the most desirable levels, significant changes were noted after only 42 days. Furthermore, the quantity of chromium (200 μg) in the daily supplement was within recommended requirements. Chromium picolinate is inexpensive and apparently nontoxic when used in the quantities described in this study. Combined with a prudent regulation of diet, the use of current lipid-reducing agents, or both, chromium picolinate may be a valuable adjunct to the treatment and prevention of heart disease.

The results reported herein are preliminary and need to be substantiated by other groups to determine the value of chromium picolinate for clinical use. Because the bioavailability of chromium is increased when coordinated with picolinate, more studies need to be done to establish the safety of chromium picolinate and to determine whether or not lower doses would be equally efficacious. Also, future studies should be done to test the effectiveness of initial higher doses followed by lower maintenance doses. Ideally, studies should compare the effect of chromium picolinate with uncomplexed picolinate as well as other forms of chromium such as chromium chloride and chromium nicotinate.

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Medical Progress

Bone Marrow Transplantation
Part II—Autologous

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Autologous bone marrow transplantation provides an effective form of "rescue" following high-dose therapy used for treating certain malignant diseases. The high doses of radiotherapy or chemotherapy, or both, should allow for greater tumor cell kill if dose-response to therapy exists for that tumor. The use of autologous bone marrow obviates the need for an HLA-identical donor, and the need for pretransplant immunosuppression; no graft-versus-host disease would ensue. We review in part II the history and background, methods of obtaining autologous stem cells, and details of the results achievable with this type of therapy. We discuss potential difficulties with autologous transplantation, as well as possible future areas of research.

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Autologous bone marrow transplantation developed from the success of allogeneic transplants. The concept, however, dates to the 1950s, when the first clinical study was published.[1] Over the ensuing several years, more than 50 such cases were reported.[2-8] These early trial results were disappointing, as they did not show improved antitumor effectiveness or that autologous bone marrow was even necessary to shorten the time of aplasia. With the encouraging results and true cures using allogeneic transplantation reported by Thomas and colleagues, interest in autologous transplantation was rekindled.[9]

Using autologous marrow obviates the need for an HLA-identical family donor (the chance of an HLA-identical donor-recipient pair being found among siblings is one in four). Autologous bone marrow transplantation also removes the need for pretransplant immunosuppression so that antitumor therapy can be based on the optimal combination of active agents. Finally, there is no graft-versus-host disease, a major source of direct or indirect morbidity and mortality. Because of these factors, autologous transplants can be offered to a larger and older group of patients.

There are several caveats. The most obvious is that when an autologous transplant is considered, the marrow should be free of the tumor cells, or at least small numbers of viable tumor cells (not detected in the bone marrow) should not substantially affect disease-free survival or cures. The tumor being treated should exhibit a steep dose-response curve to the therapeutic agent so that a higher dose will substantially increase cell kill. If one envisions cure as follows:

$$\text{cure} \propto \frac{\text{active agent(s)} \times \text{dose}}{\text{tumor burden}}$$

bone marrow transplantation allows an investigator to manipulate the dose and the active agent(s). The maximum tolerated dose with or without bone marrow transplantation may be only severalfold higher (Table 1), but an important concept is that for many experimental malignant neoplasms, a twofold increase in drug concentration may result in a tenfold greater cell kill. Also, the toxic effects from the regimen should be ablative to the marrow so the reinfusion of bone marrow becomes a necessary aspect of the therapy.

Experimental studies in animals showed conclusively the protective effect from total body radiotherapy by reinfusion of autologous marrow.[18,19] Several early studies suggested the same protective effect in humans.[3,20-24] Current excitement for autologous transplantation came from studies by the National Cancer Institute in patients with lymphoma, where Appelbaum and colleagues showed that relapsed patients with Burkitt's lymphoma could be cured by high-dose therapy.[21] Autologous bone marrow transplantation shortened the period of aplasia. From these studies of lymphoma, concepts particular to autologous transplantation have evolved, and, currently, notable efforts are directed to using autologous bone marrow transplantation in other malignant disorders.[25] To date, however, there have been no prospective randomized studies showing a benefit in favor of bone marrow transplantation. Such studies are ongoing.

Technical Aspects

The technical aspects of bone marrow harvesting have been described previously. There are, however, several steps that are unique to autologous bone marrow transplantation. First and foremost, the harvested bone marrow usually needs to be stored. Because the recipient and the donor are one and the same and the recipient needs myeloablative therapy, the marrow is stored until a later date to allow for the therapy to be administered and for any drug to be metabolized and excreted. The time period between harvesting and reinfusion of marrow may vary from several hours to months. Occasionally the period from harvest of marrow while the patient is in remission to its use at the time of relapse is several years.

Marrow viability may be maintained by proper cryopreservation and storage in ultralow temperatures. The tempera-

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TABLE 1.—*Dose Escalation Studies With Autologous Bone Marrow Transplantation*

Agent (units)	Dose: Conventional	Autologous Bone Marrow Transplant: Maximum Without	Autologous Bone Marrow Transplant: Maximum With	Limiting Toxicity
Total body irradiation (rads)[10,11]	150	350	1,000*	Lung
Mechlorethamine HCl (mg/kg)[12]	0.4	1.6	2.5	Central nervous system
Cyclophosphamide (mg/kg)[13,14]	50	200	200	Heart
Carmustine (mg/m^2)[15]	200	600	1,200	Liver, lung
Melphalan (mg/m^2)[16]	35	140	180-200	Liver, gastrointestinal tract†
Etoposide (mg/m^2)[17]	360	1,200	2,400	Gastrointestinal tract†

*Maximum of 1,400 rads in split fractions.
†Includes stomatitis.

ture of storage may range from −80° to −196°C (liquid nitrogen). A crucial step is the cryopreservation. The pluripotent stem cell must be protected from damage caused by the freezing. Cryoprotectants are agents such as glycerol or dimethyl sulfoxide.[26] Dimethyl sulfoxide is the most widely used agent today. Although the protective effect of these agents is still incompletely understood, using these agents and controlled rate freezing, minimizing the duration of the plateau of heat transition, has resulted in effective storage. Controlled cooling is thought to be very important, as the rate must be slow enough to prevent intracellular ice formation but rapid enough to prevent extracellular ice formation. This is usually achieved by cooling at 1°C to 2°C per minute using a programmable cooling chamber. There is a negligible loss of viability judged by the restoration of hematopoiesis.

Before cryopreservation, red blood cells and granulocytes should be removed because these cells are not effectively preserved and may cause clumping of the marrow. This can be achieved by various methods such as dextran sedimentation, differential centrifugation, or Ficoll-Hypaque centrifugation.

Also unique to autologous bone marrow transplantation is the attempt to remove obvious or possible contaminating tumor cells from the marrow. This process is known as purging. Various methods have been tried, all aimed at exploiting specific differences between tumor cells and normal hematopoietic precursors. Clearly the purging process must be potent enough to remove several logs of tumor cells, yet gentle or specific enough to spare the hematopoietic stem cells. Purging in experimental animal models shows a clear effect of this process on survival.[27-31]

Results of several studies have suggested that purging of the marrow is effective. Gorin, in a review of the European Bone Marrow Transplant Registry results, noted a difference in patients receiving autologous bone marrow transplant for acute nonlymphoblastic leukemia.[32] Patients' bone marrows were purged with mafosfamide. The beneficial effect mainly was significant in the group of patients who were transplanted early—less than six months after achieving a complete remission. This study was retrospective, however, using registry data of many centers that used a variety of preparatory regimens. Other investigators using either 4-hydroperoxycyclophosphamide or monoclonal antibodies without control groups have reported improved survival rates in transplanted patients.[33,34] Because of the high recurrence rate in diseases where autologous transplantation has been used, the contribution of purging may be difficult to establish.

Another unique aspect to autologous transplantation is the use of peripheral stem cells. Animal studies using dogs have shown the protective effect of peripheral blood mononuclear cells against lethal myelotoxicity.[35] In 1979 Goldman and co-workers reported successful autologous peripheral stem transplantation in patients with chronic myelogenous leukemia.[36] Failures were also reported at that time. Encouraged primarily by the animal experiments, the University of Nebraska group and several other centers continue similar efforts in humans.[37] Unfortunately, there is no good assay for the true stem cell except for in vivo proof of engraftment. Assays such as granulocyte macrophage colony-forming units measure hematopoietic precursors and not the activity of the true stem cell. This assay and the number of mononuclear cells are useful as relative indicators of the number of stem cells. The in vivo data are becoming available and clearly support the experience from the laboratory. Peripheral stem cells, especially when collected at the time a patient is recovering from standard chemotherapy, are able to fully reconstitute the marrow of patients who have had myeloablative therapy. In fact, the time to engraftment from these peripheral cells is shorter than when using marrow. The average time to 500 granulocytes per microliter is approximately two weeks.

The idea of autologous peripheral stem cell transplant has several attractive features. Cells can be collected by repeated apheresis, and there is no need for marrow harvesting and possible general anesthesia. This is especially useful for some patients who have no harvestable marrow, such as patients with Hodgkin's disease or lymphoma after pelvic radiotherapy. Autologous peripheral stem cell transplants may also allow transplantation for patients with possible marrow disease, such as those with Hodgkin's disease with fibrosis of the marrow and possible marrow involvement. Whether clonogenic tumor cells circulate freely in the peripheral blood and are also collected is unknown at this time. In cases of failure from transplantation, the sites of relapse are usually in areas of previous disease, suggesting that persistent disease and not reinfusion of tumor cells accounts for the recurrence.[37] The malignant cells in circulation may not have a high fraction of clonogenic cells and thus may be less able to establish recurrent disease. Furthermore, freezing and thawing may contribute to more selective removal of the tumor cells when or if they are present in small numbers. There are reports of apparent tumor cells being found in normal marrow collected in patients for breast cancer and lymphoma when the marrow was grown in long-term cultures.[38] Whether these represent especially virulent cells or possibly artifacts of long-term cultures remains to be determined.

Results

What, then, are the results with autologous bone marrow transplantation? The answer to this question will depend on how autologous transplantation is used. One can envision using autologous transplantation for various reasons:

- To deliver curative amounts of active agent(s) that would otherwise not be possible because of marrow toxicity;
- To determine the nonmyeloid dose-limiting toxicity of single agents and antitumor activity; or
- As "rescue" to prevent cumulative toxicity to bone marrow because of prolonged exposure to conventional chemotherapy.

Beginning with the third point, using autologous marrow as "rescue" for conventional therapy has been tried. The cell dose used was not specified but seemingly resulted in only minor delays in therapy and, thus, good dose intensity.[39] Whether this is an important effect applicable to a variety of patients remains to be determined.

Using autologous bone marrow transplantation to determine the nonmyeloid dose-limiting toxicity of single agents and potential antitumor activity has been a crucial step in developing a rational therapeutic protocol. The use of single agents allows the determination of the nonmyeloid dose-limiting toxicity (Table 1). These single agents, usually used in phase I or II trials, allow the evaluation of antitumor activity such as of carmustine (BCNU) therapy for central nervous system tumors and melphalan for neuroblastoma and melanomas.[15,16] As shown in Table 1, the increment of each single agent achievable with autologous bone marrow transplantation is modest, and such increments are unlikely to achieve a notable effect on cure rates when used alone in resistant tumors. With this knowledge, however, an investigator can then combine drugs rationally, exploiting the optimal combination of active agents with different limiting organ toxicity. These toxicity data are not available from conventional doses of the listed agents. Note, however, that the "maximum" dose without autologous bone marrow transplantation allows the severe pancytopenias to occur, lasting no more than three to four weeks. Thus, it is unlikely that combinations of the maximum doses of the drugs with or without radiation would consistently allow for recovery without bone marrow transplantation.

The results of autologous transplants used to deliver curative concentrations of active agents are the most promising in clinical trials. Most of the diseases will be discussed individually.

Lymphomas

Diffuse large cell lymphoma. In the 1970s Appelbaum and colleagues did bone marrow transplantations in eight patients with non-Hodgkin's lymphoma, using the standard preparative regimen consisting of total body radiotherapy and cyclophosphamide. In one study all patients had advanced refractory disease and had failed earlier therapy.[40] All but one achieved a complete response, and three of the eight are still alive and in complete remission. These data gave impetus to several other trials in bone marrow transplantation for lymphoma using allogeneic and autologous bone marrow with or without irradiation. Autologous bone marrow transplantation was used with Burkitt's lymphoma patients, resulting in more rapid recovery of peripheral blood counts.[21,41] The cumulative experience from the literature still only represents several hundred patients, although the number continues to grow exponentially. From these early studies, several concepts have evolved. The major one is that of tumor responsiveness. Various groups have shown that a so-called sensitive relapse patient—that is, a relapsed patient who is still responding to conventional therapy—does significantly better than a patient who is in resistant relapse—refractory to second-line therapy. Similarly, the lower the tumor burden before ablative therapy, the more likely it is that the outcome will be favorable.

Recently reported results have been encouraging. Several groups from the Dana Farber Cancer Center (Boston), Memorial Sloan Kettering (New York), Lyon (France), the University of Nebraska Medical Center (Omaha), and MD Anderson Cancer Center (Houston) have reported excellent survival rates and probable cures in patients with relapsed lymphomas (predominantly diffuse large cell) ranging from 65% to 70%, with follow-up periods of two to four years.[34,42,43] Furthermore, transplantation has been used in this group of patients in an "adjuvant" setting. That is, retrospective analysis is used to identify risk factors for relapse. These factors are then used if a patient currently on therapy has a high likelihood of relapse. In such patients, once a maximum response or a complete response has been achieved, transplantation can be used with the goal of helping the patient achieve a cure. In the study by Gulati and colleagues from Memorial Sloan Kettering, autologous transplantation did accomplish this, taking a group of patients with historically about a 20% to 30% chance of cure and improving the actuarial disease-free survival to approximately 80%.[41] One caveat is that patients in several of the studies were carefully selected, and part of the inclusion criteria was a responsive relapse or the achievement of a "minimal disease state." Thus, other patients who did not achieve a minimal disease state were not eligible. If these patients are included in the calculation, the data may approach results reported using second-line conventional chemotherapy for relapsed patients. This selection bias should not, however, detract from the excellent results achieved for this specific high-risk group of patients. Only a prospective randomized trial comparing transplantation with continued conventional chemotherapy will determine the best therapeutic option.

Hodgkin's disease. Autologous bone marrow transplantation for Hodgkin's disease is now a highly successful treatment for patients who have failed first-line chemotherapy. Before autologous transplants were available, the optimal management for patients failing the primary use of mechlorethamine hydrochloride, Oncovin, procarbazine hydrochloride, and prednisone (MOPP) therapy or for those who did not achieve a complete response, was to use a second-line, non-cross-resistant regimen, usually doxorubicin (Adriamycin) hydrochloride, bleomycin sulfate, vinblastine sulfate, and dacarbazine. In the Stanford experience, however, the freedom from progression was only 20% in complete responders and only 9% if all patients were analyzed. Encouraging results have been obtained for these patients with autologous transplantation, including those patients who fail second-line or further chemotherapy and clearly represent a poor prognostic group. Various investigators have done autologous transplants for such patients and found a disease-free survival rate of 25% to 70%.[44-46] When the MD Anderson and University of Nebraska group evaluated their

data, they were able to subdivide the patients into high-risk and low-risk groups. Those patients with good performance status, low tumor burden, and having previous therapy with two or less drug combination regimens had a freedom from progression of approximately 80% at four years; most of these patients are probably cured.[47] Again, a word of caution: comparing autologous bone marrow transplantation data with chemotherapy is necessary because there is usually an age limit with transplantation. Further carefully designed studies with larger numbers of patients are necessary to confirm these results. It is still unclear whether the concept of tumor responsiveness applies to this group of patients.[46] For Hodgkin's patients who have had previous mantle radiotherapy, a preparative regimen should not contain total body irradiation, since further radiotherapy leads to substantially increased pulmonary toxicity.

High-grade lymphomas. Burkitt's lymphoma is historically important because it was one of the first tumors clearly curable with chemotherapy. Despite its sensitivity to chemotherapy, survival rates are dismal in patients with advanced or relapsed disease. Encouraged by the results of allogeneic transplants for leukemias and the similar high growth fraction of Burkitt's lymphoma, investigators attempted autologous transplantation. A remarkably high response rate was noted when the dose of chemotherapy was increased with autologous transplants compared with the resistance observed at conventional doses. Long-term survival and probable cure in these early patients left no doubt about the efficacy of this treatment. Although the total number of patients receiving the procedure is relatively small, the overall survival rate in those with poor prognostic factors is approximately 50% to 70%.[21,41,48] Autologous bone marrow transplants for high-risk lymphoblastic lymphoma also have had encouraging results.[49,50]

Other lymphomas. Autologous bone marrow transplantation to treat other lymphomas such as follicular small cleaved cell and diffuse mixed cell have also been done. Likewise, patients with low-grade lymphomas that transform to a higher grade lymphoma have also received transplants. Some of the results are encouraging, but the number of patients is still too small for any meaningful conclusions.

Leukemias

Intensive ablative regimens have also been tried in autologous transplantation for acute leukemias such as those successfully treated with allogeneic bone marrow transplantation. Leukemia, as a disease of the bone marrow, makes autologous transplantation difficult. Assuming no major immunologic changes in the bone marrow by the processing method, one would not expect the results of autologous transplants at best to be very different from identical twin transplantation, which carries a high relapse rate of approximately 50% to 60%.[51] The high relapse rate reflects an inadequate preparative regimen and the lack of a graft-versus-leukemia effect. Newer preparative regimens should lower the relapse rate. Clearly, the primary concern of autologous bone marrow transplantation for leukemia is reinfusion of clonogenic cells. The assumption is that when marrow is harvested from a patient in complete remission, it is contaminated with a small number of leukemic cells. The mechanical handling and the freezing and thawing may eliminate a good fraction of these cells, and small numbers reinfused may not necessarily lead to leukemia relapse. Several pilot studies have been done with encouraging results.[52-57] When autologous transplantation is done for acute nonlymphoblastic leukemia in first complete remission, the overall results show an approximately 35% to 50% chance of disease-free survival. These results may be favorably biased by the timing of the transplant, such as doing the transplant several months after the patient has remained in complete remission, or by other selection factors. Prospective studies are needed to confirm the early encouraging results comparing allogeneic bone marrow transplantation with continued intensive chemotherapy. Investigators at Johns Hopkins University (Baltimore) have reported promising results with autologous transplantation for treating acute nonlymphoblastic leukemia patients in second or subsequent complete remissions.[33] In these studies using 4-hydroperoxycyclophosphamide purging, a 28% disease-free survival rate at four to five years has been reported—a good outcome in a group of patients with a very poor prognosis.

Autologous transplantation for acute lymphoblastic leukemia has also been tried. The results so far have been discouraging and do not seem to be significantly different from those attained with intensive chemotherapy.[58]

Solid Tumors

A clear advantage to using autologous transplantation is dose intensity. Several studies have suggested a steep dose-response curve for irradiation and chemotherapy in patients with breast cancer, making this disease a likely candidate for autologous bone marrow transplantation. A recent review of the available data has been published by Antman and Gale.[59] It is clear that in unfavorable groups of patients, the results are encouraging, but it is still quite early. The important point is that using intensive therapy does achieve higher complete response rates.

In 1988 Peters and associates reported early data on using autologous transplantation in ten breast cancer patients with a highly unfavorable prognosis.[60] These were premenopausal women with more than ten positive lymph nodes. In such patients, there is usually a median time to relapse of a year and a survival of only three to four years. They were initially treated with cyclophosphamide, doxorubicin, and fluorouracil (CAF). Bone marrow was then harvested and one more cycle of CAF given. Following this, patients were prepared with high doses of cyclophosphamide, cisplatin, and carmustine. They then received their stored bone marrow. All ten patients survived the transplant, and none have relapsed; however, the median follow-up time is still less than a year. This promising result indicates that this therapy may have a notable effect in curing such patients.

A second type of tumor where autologous bone marrow transplants have been shown to be effective is neuroblastoma, one of the most common childhood malignant tumors. In children older than 1 year with neuroblastoma, 70% have stage IV disease, which is fatal in 90%. Initial studies using high-dose melphalan and autologous bone marrow transplantation showed some promise.[61-63] Stimulated by these early results, several groups used autologous transplantation following aggressive surgical procedures and chemotherapy. Pinkerton and co-workers carried out a randomized study with the European Neuroblastoma Study Group and reported a significant improvement in disease-free survival rates in those patients who received high doses of melphalan and autologous bone marrow transplantation.[64] With follow-up

of as long as 48 months, the disease-free survival plateau for transplanted patients is at approximately 40%, compared with 20% for those patients not receiving transplants.

Several other tumors have also shown some response to transplantation. These include sarcomas,[65] melanomas,[66] small-cell lung cancer,[67,68] colon cancer,[69] and multiple myeloma.[70,71] These trials have been done with small numbers of patients and have not shown a significant effect on disease-free survival rates yet.

Future Directions

Clearly the earlier use of autologous transplantation as adjuvant therapy will have a greater effect and likely more meaningful results. Autologous transplants earlier in the clinical course of the underlying diseases have already been done with hematolymphoid disorders and should also affect response rates in patients with solid tumors. Well-designed, prospective, randomized studies are still lacking, however.

New combinations of active agents, including drugs and cytokines such as interferon or interleukin 2, used either as part of the preparative regimen or potentially as immunomodulators, may affect the outcome of autologous transplants. Other immune system manipulation such as adoptive transfer with lymphocyte-activated killer cells or tumor-infiltrating lymphocytes may also contribute to a more favorable outcome. Recently, Santos and colleagues reported the induction of what appears to be graft-versus-host disease in patients with autologous transplants who are taking cyclosporine. If this graft-versus-host disease is limited to a mild clinical manifestation and associated with a graft-versus-tumor effect, it could contribute to a lower relapse rate.[72]

The reported isolation of the mouse hematopoietic stem cell by Weissman's group[73] has been very exciting, and the hope is justified that the human stem cell will also soon be isolated. The availability of the human stem cell would be an important step forward for autologous bone marrow transplantation, lessening the concern of reinfusion of tumor cells, as presumably stem cell markers will not be found in tumor cells.[74]

The use of cloned growth factors may reduce morbidity and mortality from prolonged neutropenia but may also aid selection of a subgroup of patients for transplantation. That is, current dose intensity may be achievable without transplantation. Potentially, a larger number of patients may be curable without transplants.

Finally, as investigators understand better the toxicities and indications for autologous bone marrow transplantation, the patients' burden in terms of physical, psychological, and financial costs should lessen substantially.

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Specialty Conference

N-of-1 Clinical Trials

A Technique for Improving Medical Therapeutics

Discussant
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This discussion was selected from the weekly Grand Rounds in the Department of Medicine, University of Washington School of Medicine, Seattle. Taken from a transcription, it has been edited by Paul G. Ramsey, MD, Associate Professor of Medicine, and Philip J. Fialkow, MD, Professor and Chair of the Department of Medicine.

ERIC B. LARSON, MD*: Most clinicians have a keen interest in therapeutics and especially therapeutic efficacy. In fact, medical therapeutics can be viewed as a series of therapeutic experiments as follows:

A				*B*
Initial State	→	Therapy	→	Subsequent State

The patient comes to the physician in an initial state, *A*, and is offered treatment. The patient then assumes a subsequent state, *B*.[1] If *B* is more desirable, we typically judge that therapy was effective. If *B* is no different or is less desirable, we judge that therapy made no difference or was ineffective. Although this account seems straightforward, such simple assertions may not be true because of confounding factors.[2]

Effectiveness may be overestimated because of several factors. First, a patient can recover spontaneously coincident with treatment, an especially well-known occurrence for self-limited conditions. Second, patients commonly present when their symptoms are worse, especially patients with a chronic disease. Coincidental treatment appears to cause the problem to subside when the patient has simply returned spontaneously to the average, so-called baseline state of a chronic disease. This has been referred to as "regression toward the mean."[3] A third factor that may lead to an overestimation of effectiveness is a placebo effect. For some therapies, as much as 30% or more of the benefits may be due to the well-known placebo effect.[4] Finally, the expectation of a beneficial response and a willingness-to-please effect[5] are related to the placebo effect. In many patients, the simple "expectation" that a treatment will be beneficial may often be sufficient to promote a beneficial effect. The willingness-to-please effect results from the so-called obsequiousness bias[5] in which a patient gets better to please an expectant physician.

Similar confounding forces can obscure therapeutic effectiveness. Coexistent illness can coincidentally exacerbate the underlying problem. Chronic diseases have spontaneous exacerbations, and when these occur coincident with treatment, it appears that therapy is ineffective. Malingering or a secondary gain in which the patient experiences benefit from not getting better can make a patient resistant to the true effect of treatment. An age-related (physiologic) decline superimposed on a beneficial treatment effect may combine to cancel each other. Finally, if an incorrect diagnosis has been made, treatment will appear to be ineffective. For example, if a patient's symptoms or signs represent the upper or lower limits of a normal variation, then the treatment received, although usually effective, is ineffective in the misdiagnosed case.

Randomized Clinical Trials

Fortunately, randomized clinical trials (RCTs) have been used to evaluate medical therapeutics since the late 1940s.[6] Because such trials help eliminate the confounding factors outlined above, they have become the gold standard by which clinicians judge therapeutic efficacy. An RCT allocates consecutive patients to different treatments or randomly allocates the order of treatment in crossover experiments. When done carefully with enough patients, the randomization eliminates bias that might confuse the interpretation of the therapeutic experiment.

Unfortunately, many of a clinician's day-to-day treatment decisions cannot be based on the results of randomized trials. Table 1 shows examples of situations or problems in which RCTs may not be appropriate for making therapeutic choices. Unavailability of randomized clinical trials may be encountered in the case of a rare or unusual disease. Randomized trials may also not be available for some older treatments and for newer or novel treatments. Because RCTs have been widespread only since 1970, older treatments were often not evaluated by them. Newer or novel treatments, especially those devised by clinicians for single patients, are typically not subjected to randomized trials.

Even when there are good randomized trials showing efficacy, several factors limit their generalizability to a specific patient. For example, the patient might be outside the eligibility requirements for entry into an RCT. Eligibility criteria for most trials are so restrictive that less than 10% of patients with the disease in question may be accepted. Not surprisingly, the patients who are excluded are the ones in whom therapeutic dilemmas and an evaluation of therapeutics are often the most troublesome. Thus, their omission

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TABLE 1.—*Limits of Randomized Clinical Trials (RCTs) for Care of Individual Patients*

RCT unavailable or impossible
Good RCTs show benefit but may not be generalizable
Eligibility criteria too restrictive
Some patients are nonresponders
Side effects
Good RCTs show *no* benefit but may not be generalizable
Atypical patients
Treatment response is idiosyncratic

from RCTs allows investigators to assess efficacy with fewer complicating factors. Another problem arises from the fact that even though a randomized trial has shown efficacy, not all patients will benefit from treatment. In addition, some patients may experience enough side effects that the net effect of treatment is harmful. The single patient who does not have a beneficial response experiences that event with 100% certainty even when generalizations based on populations studied by RCTs indicate the net effects are likely to be beneficial.

There are also limits to the generalizability of RCTs that show no apparent benefit. Good randomized clinical trials may not show any net benefit, but an individual patient may still benefit from treatment, especially if the treatment has biologic plausibility. Some RCTs have inadequate sample sizes and, hence, inadequate statistical power to show efficacy.[7] An individual patient could also be an atypical responder, or responsiveness to treatment may be idiosyncratic and difficult to demonstrate by an RCT.

In summary, even though randomized clinical trials are widely used for assessing therapeutic efficacy, their results may not apply to single patients or they may be unavailable for certain treatments, thus leaving clinicians in a quandary about therapeutic efficacy. Because of this quandary, there is increasing interest in single-patient experiments. A number of terms have been used to describe single-patient experiments, including N-of-1 trials, single-patient clinical trials, single-case analysis, crossover and self-controlled research designs, and single-patient RCTs. The field has an interesting history and holds great promise for improving the science of medical therapeutics.

Case Reports

Because case reports can be useful ways to illustrate valuable clinical lessons, I will present three single-case analyses in the order of my exposure to them. The first, a "case report" presented at the American Federation of Clinical Research meetings in 1985, was the case that piqued my interest in single-patient trials.[2] The second, a classic case that occurred at the interface of the developing science of statistics and popular culture, is intriguing for both its contents and the statistical power of its design.[8] The final case illustrates a single-case clinical trial that, although not random and only "single blinded," was convincing and influential.[9]

The first case was reported by Guyatt and co-workers from McMaster University, Hamilton, Ontario.[2] The patient, a 65-year-old man with uncontrolled asthmatic bronchitis, was becoming progressively more disabled by dyspnea with even simple daily activities. His therapeutic regimen eventually consisted of albuterol inhaler, ipratropium bromide, theophylline, and daily doses of prednisone. The clinician and the patient were uncertain whether the theophylline or ipratropium therapy was beneficial. Both suspected that theophylline was helpful and ipratropium was not. To optimize the therapeutic regimen, a single-patient trial was designed. Either theophylline or placebo, in a random order, was given for ten-day crossover periods. Three 10-day crossover pairs were planned. The end points included dyspnea, the need for albuterol inhaler, and the amount of sleep disturbance. During the first period, the patient did better than during the second ten days of the crossover trial. The same pattern then appeared during the second crossover period. The trial, which was originally scheduled to go for three crossover periods (about 60 days), now seemed too long to both the clinician and the patient. Both agreed that the trial should be terminated, presumably to allow the patient to resume taking theophylline. They were surprised when the placebo was associated with scores indicating increased well-being. Based on a review of the literature and the patient's course, it was determined that the seemingly anomalous results were most likely explained by gastroesophageal reflux (a xanthine side effect) and aspiration.[10] The theophylline therapy was stopped, and subsequently an N-of-1 trial of ipratropium revealed the beneficial therapeutic effects of its use. Eventually the patient was treated with a regimen of albuterol and ipratropium. He then tolerated a prednisone taper so that he could comfortably complete most of his activities of daily living on a regimen of 10 mg of prednisone every other day.

The second "case report" is not a medical case but represents a particularly famous single-case experiment. The case was an important one in the development of principles of experimentation and illustrates some useful points about randomization and statistical power. In 1935, R. A. Fisher, a British statistician whose name is most often linked with multiple-subject experiments, reported an example of how to conduct an experiment with a single subject and used that example to explain basic notions that underlie all experiments. This was the "lady tasting tea experiment."[8]

The case involved a tea-drinking English woman who claimed that she could tell whether the tea was added to the milk or the milk was added to the tea. Four cups of tea were prepared one way and four cups the other way, and the eight cups were then presented to her in a random sequence. She was told in advance that she was to identify the four cups that were prepared each way. The lady correctly identified all eight cups, and the P value was determined by the randomization test procedure. The null hypothesis was that her response at any treatment time was the same as it would have been at that time if any of the other cups had been presented. There are $8!/4!4! = 70$ ways in which eight cups can be presented with respect to milk first or tea first, given that four cups were milk first and four tea first. Thus, Fisher computed the P value as 1/70 because only 1 of the possible sequences of 4 Ms and 4 Ts correctly matched the woman's responses ($P = .014$).

An important feature of this experiment, in contrast to the first case report, is that the randomization occurred in blocks of eight treatments, not blocks of two as in the typical crossover experiment. Thus, the statistical power was considerably greater.

The third case report is a more primitive example of a single-patient trial.[9] Nonetheless, it also shows the value of single-patient experimentation. The report entitled "Inter-

nal-Mammary-Artery Ligation for Coronary Insufficiency—An Evaluation" was based on a presentation made in 1957 to the New England Surgical Society. This topic would later be investigated in a widely quoted article from the University of Washington describing a randomized, single-blind trial that compared a sham operation with internal mammary ligation.[11] Ralph Adams, MD, in the 1958 paper,[9] reported four cases, one of which was of a 60-year-old man admitted "three days after occurrence of his known episode of coronary thrombosis."

> His case was well known to the hospital because of previous attacks of deep thrombophlebitis, pulmonary embolism and hypercholesterolemia, and prior episodes of coronary occlusion. Precordial pain was intense and he was apprehensive that he would die. He was a highly educated man, well informed for a layman, on medical matters and in a position of considerable community responsibility. Admission was for the specific purpose of altering internal mammary circulation in the hope of giving him some cardiac protection. He was told . . . that this procedure was currently being widely discussed and, in some quarters, enthusiastically recommended. He was also informed that the hospital was in the process of evaluating the procedure as definitely as possible. These background facts led him to request that the operation be tried in the hope that he might be helped. . . .
>
> At operation, on the day of admission, a short incision was made in the second intercostal space lateral to each sternal border and each internal mammary artery was exposed. A silk ligature was placed about each artery but neither was tied. Thus, only a first-stage operation had been done, consisting of a skin incision and encirclement but not ligation of the internal mammary arteries.
>
> On awakening from the brief and light anesthetic, the patient reported that he was free of pain. He has had no pain since that date. An electrocardiogram on the day after operation showed no detectable change from preoperative tracing. Two days after the operation the ligatures from the internal mammary arteries were tied. Subsequent electrocardiographic tracings gave no evidence of improvement.

The author goes on to describe follow-up, which included no recurrence of symptoms, and states that

> in this case, there was not a fair chance to assay the relief of symptoms to be obtained by internal mammary artery ligation because the patient lost all symptoms after the first portion of a staged procedure that he believed to be the completed operation.

Adams reported what we would call a nonrandomized single-patient crossover experiment. A sham operation was followed by a real operation—dramatically showing what many might now call a placebo effect of internal mammary exposure.

Formation of an N-of-1 Clinical Trial Service

Before establishing a single-patient trial service, we contacted Dr Gordon Guyatt, who has actively investigated single-patient trials. He provided us with great encouragement and a summary of the experience of an N-of-1-trials service at McMaster University.[2] Most of his trials had been in the subspecialties of pulmonary medicine and rheumatology. Of the first 42 trials done at the center, 29 gave definitive results. In 11, active treatment was found to be effective, in 17 it was ineffective, and in 1 it was harmful (the theophylline case). Eight other trials gave less definitive results. Five were judged unsuccessful, three because, despite definitive outcomes, the results did not lead to action (G. Guyatt, written communication, June 1987).

Based on this encouraging report, we submitted a small grant proposal to the National Center for Health Services Research. Our research group, which includes Allan Ellsworth, PharmD; Jim Nuovo, MD (family medicine); Ina Oppliger, MD (rheumatology); Gerald van Belle, PhD; and Alice Arnold, MS (biostatistics), is now funded to establish and evaluate a single-patient trial service. We have announced our intentions to workers in other specialties and are currently receiving patients.

Because the objective of the "N of 1" experiment is to find the best treatment for a particular patient, we and others believe that some of the ethical questions asked of the standard randomized trial no longer apply.[2] For example, does the potential benefit to other patients outweigh the possible risk to this patient? Nonetheless, three ethical requirements do apply. First, a patient's free and informed consent should be requested after the clinician has described every feature of the trial that would materially affect the patient's decision to take part, including the reported effectiveness and safety of alternative treatments, the treatment targets to be used, and the duration and number of treatment periods to be executed. The second ethical requirement is that a patient must be free to withdraw at any time without loss of care. The third is that the same degree of confidentiality applied in other clinical situations must apply to the study results. One of our first tasks as an N-of-1 clinical trial service was to approach the Human Subjects Committee (Institutional Review Board) and seek approval for pending single-patient trials. They have developed an expedited approval process that facilitates the prompt institution of clinical trials.

When to Do a Clinical Trial

Perhaps the most germane issue in single-patient trials is when to do them. That is, when is a patient most likely to benefit from the results of a single-patient trial? The most important issue here is whether there is doubt about efficacy. Doubt may occur because neither the patient nor the physician is certain an existing treatment is working. In this setting, a patient with a chronic disease may be doing poorly or not improving on a medication regimen that could also be causing side effects, as exemplified by the theophylline case.

Another instance when efficacy may be in doubt is during the institution of a new treatment. Here the patient is being offered a new drug and the question is, "Will it work?" The clinician may be uncertain when the literature is equivocal about the drug, the risk-to-benefit ratio is less favorable, or the patient is reluctant to comply with presumably efficacious treatment.

For patients with rare or unusual conditions, the use of the single-patient trial may not only benefit the patient but also add to knowledge about the management of unusual conditions. The literature contains numerous examples of single-patient experiments where treatments of conditions like familial Mediterranean fever and narcolepsy were evaluated with N-of-1 trials.

Doubt about efficacy may be a motivating factor for a single-patient trial also when a patient insists on a treatment as necessary or effective in contradiction to medical advice or practice. The single-patient trial can be used when the physician is unable to convince the patient otherwise. In this case, a negative clinical trial should not surprise the physician but may be convincing to the patient.

After determining whether therapeutic efficacy is in doubt and deciding whether one wishes to demonstrate efficacy or a lack thereof, the clinician will need to consider other questions that affect the feasibility and worth of a single-patient trial. First is whether a treatment will likely be long term. Given the time required to conduct such a trial, single-patient trials of short-term therapies tend not to be

worth the effort required of the patient, and they are less likely to have value for the individual patient unless the patient will require the short-term treatment repeatedly.

Several questions related to the pharmacokinetics of a possible therapeutic agent affect the logistics and ease of doing single-patient trials.[12] The ideal treatment for single-patient trials is one that can be rapidly started and stopped. Thus, outcomes can be assessed starting relatively early in the trial, and there is little or no carryover between treatment periods. When these criteria are not met, carryover or period effects may complicate the interpretation.[12] These effects may require trials that are much more time consuming (for example, involving washout periods) or involve special design modifications. In general, single-patient trials are less likely to be useful for curative treatments (so-called period effects) or for long-acting treatments (due to carryover effects).

How to Do a Clinical Trial

There are three critical components of the single-patient trial: randomization, blinding of patient and physician to treatment assignment, and defining and quantitating the outcomes. The last, establishing explicit criteria for evaluating the efficacy of treatment, is a feature of the single-patient trial that is also important for medical therapeutics in general.

Randomization is necessary to minimize systematic biases that will occur related to the order of treatment and to permit double blinding to occur. Randomization is usually accomplished in a crossover style, that is, in blocks of two. If, however, it is predetermined that four, six, or eight trials will be done, the statistical power of the trial is improved considerably by randomization in larger blocks.[13] For example, when six trials are planned, the possible P values range from .125 for the paired experiment in which three crossover pairs occur ($[1/2]^3$) to .03 when all six trials are randomized independently ($[1/2]^6$). Intermediate values are possible when constraints are added.

Blinding is a key element to minimize observer-induced bias. In most single-patient trials, the patient records symptoms and, in some cases, signs. Ideally both patient and physician are blind to the treatment assignment. Records of assignment are kept with one of the trial service staff and, if a drug is involved, the pharmacist who has prepared the treatment packages.

Single-patient trials require that the goals of treatment be explicitly identified at the time the patient enters the trial. Ideally, three to five key variables are determined. The variables may reflect disease activity or symptom severity. Usually the most important variables measure patient functioning, reflecting the value of treatment for the patient. In the ideal case, outcomes would include the measurement of a physical sign, a subjective or objective rating of performance in conjunction with, for example, a laboratory measurement reflecting disease activity. The patient's goals must be assayed to be certain that the measures of performance are compatible with the patient's wishes, especially regarding quality of life.

Systematic measurement of a limited number of variables is important for a successful single-patient trial. We typically use self-administered questionnaires that rely on 7-point Likert scales or tabulate the frequency of events. We also teach patients to measure biologic variables like the forced expiratory volume in one second, peak flow, and walk time. We have found it easier to use 7-point Likert scales than visual analog scales. In the standard crossover design, the patient can be asked to state a preference for one treatment period compared with the other.

There are other issues that must be solved when designing a clinical trial. A critical question is the duration of treatment. In general, we believe the old adage, "shortest is easiest." Treatment often takes longer than expected, however, because time is required for peak effects to develop or for treatment effects to dissipate. For drug regimens that are rapidly started and stopped, treatments can be shorter and a random block design of six or eight trials of active drug and placebo can be evaluated in less than two weeks.

A special case occurs when a drug is being used to minimize or prevent attacks or exacerbations of a recurrent disease. To determine duration, the frequency of exacerbation needs to be estimated. Given a reasonable estimate of the frequency, the duration can be based on the "rule of 3s." This rule states that if an event occurs once every x days, the duration of observation must be three times x days to be 95% certain to observe one event. In the case of familial Mediterranean fever where an attack may occur once every two weeks, the treatment period would need to last six weeks to be reasonably certain to observe an effect.

Another question that affects the duration of the trial is how many pairs or trials are needed. The answer to this is the tautology, "as many as are needed." In some trials, we have recommended that a single pair may provide an adequate demonstration of efficacy. Such a demonstration lacks statistical power, but the demonstration of effect may be so compelling as to convince both patient and physician that efficacy is no longer in doubt. On the other hand, when the probability of a treatment being effective is about 50% before the

TABLE 2.—*Posterior Probabilities as Function of Prior Probabilities and Likelihood Ratio*

Prior Belief Treatment Is Effective, P	*Likelihood That Treatment Is Better Than Spontaneous*	*Patient Improves*	*Posterior Probability, P*
.01	3	Yes	.030
	5	Yes	.051
	1/3	No	.003
	1/5	No	.002
.10	3	Yes	.25
	5	Yes	.55
	1/3	No	.032
	1/5	No	.022
.50	3	Yes	.75
	5	Yes	.83
	1/3	No	.25
	1/5	No	.17
.80	3	Yes	.92
	5	Yes	.95
	1/3	No	.57
	1/5	No	.44
.90	3	Yes	.96
	5	Yes	.98
	1/3	No	.75
	1/5	No	.64
.95	3	Yes	.98
	5	Yes	.99
	1/3	No	.86
	1/5	No	.79

trial, and there are major risks of side effects, anything short of a statistical certainty may not be satisfactory. In the case of a paired crossover trial, the binomial distribution suggests that after four trials, the probability of treatment being repeatedly favored over placebo is .5 after the first trial, .25 after the second trial, .125 after the third trial, and .0625 after the fourth trial, which is $(1/2)^4$.

In general, the issue of "statistical" certainty—the mythical $P < .05$—is less critical in single-patient trials. An interesting perspective is added by assaying the clinician's estimate of the likelihood of success in that patient (the prior probability) and determining the estimated likelihood that the treatment is efficacious based on the literature. Using a Bayesian analysis, a posterior probability based on the patient outcome in a single-patient trial can be calculated as shown in Table 2 (G. van Belle, written communication, June 1987). These posterior probabilities show the effect that a single-patient trial can have on a clinician's level of certainty that treatment will be helpful for a patient.

Conclusion

We formed the trial service to simultaneously establish, demonstrate, and determine the value of single-patient trials in clinical practice and to help do the clinical trials. Our involvement ranges from being limited consultants providing study drugs and simply reviewing the protocol, to providing detailed, in-depth consultation regarding the value of a clinical trial in a particular patient, developing a study design, interviewing the patient, developing target outcomes, printing forms, preparing placebo drug and outcome forms, and doing follow-up. In all cases, we provide an interpretation of the results of the trial and are anxious to learn how the trial was used in clinical decision making and practice.

In summary, single-patient clinical trials can be used to improve the efficacy of treatment—especially long-term treatments and treatments with uncertain efficacy or a risk of serious toxic effects. Examples of suitable conditions for study are numerous, including common problems such as chronic obstructive lung disease, osteoarthritis, recurrent headache and other chronic pain syndromes, "fibrositis" or fibromyalgia, and agitation in demented patients. We have done trials in these common conditions and have also investigated more unusual and complex problems such as progestational drug side effects, treatment of the "restless" leg syndrome, and treatments of orthostatic hypotension. The principal benefits are an increased certainty for patients and their physicians that a treatment is worth pursuing because it is effective or should be abandoned because of an absence of a net benefit.

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Medical Staff Conference

Physician Risk and Responsibility in the HIV Epidemic

Discussant
MOLLY COOKE, MD

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Homer A. Boushey, MD, Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

CAROL MANGIONE, MD*: *Molly Cooke, MD, is a well-known member of our faculty. After completing medical school at Stanford (California) University, Dr Cooke came to University of California, San Francisco, for residency training in medicine and served as Chief Resident in Medicine at San Francisco General Hospital Medical Center (SFGH) before becoming a Kaiser Family Foundation fellow in general internal medicine and then a member of the general internal medicine division at SFGH. Dr Cooke has received many awards for her clinical teaching and has focused her research on improving clinical teaching and, more recently, on the attitudes of medical residents caring for patients with AIDS. She also chairs the Ethics Committee at SFGH. Her research interests and clinical experience make her eminently suited to discuss this conference's topic, the rights and duties of physicians in the care of patients infected with the human immunodeficiency virus.*

MOLLY COOKE, MD†: Epidemic disease reliably produces consternation in the populace and among physicians. The acquired immunodeficiency syndrome (AIDS) has been no different; examples of physicians reluctant to care for patients infected with the human immunodeficiency virus (HIV) date from the earliest days of the epidemic. In early 1982, the chief medical resident at SFGH was telephoned by an emergency department physician in a medically sophisticated community located several hours away from San Francisco by car. The physician was seeing a young man with cough and fever in whom he suspected *Pneumocystis carinii* pneumonia. He requested permission to transfer the patient by ambulance to SFGH, using the experience of the medical center and the best interests of the patient to justify the request. The physician also noted that "we have a clean hospital and don't take care of people like this." The patient was severely hypoxemic; the chief resident, therefore, considered him unstable for transfer and declined permission. He offered instead to arrange a telephone consultation for the inpatient physicians at the first hospital. Despite an agreement to this end, the patient arrived in San Francisco four hours later in a private automobile with a portable oxygen tank that had long since expired and a partial oxygen pressure of 48 mm of mercury, having been refused admission at the original hospital. Other early examples of a reluctance to care for AIDS patients on the part of medical students, house officers, and attending physicians included adopting extreme infection control precautions (P. Klass, "The Age-Old Fear of Contagion Arises When Treating an AIDS Patient," *The New York Times,* October 25, 1984, p C2) and refusing to do postmortem examinations.[1]

The initial phase of concern over the rights and responsibilities of physicians affected those caring for patients with symptomatic HIV infection, particularly internists, oncologists, infectious disease specialists, family practitioners, emergency department physicians, and pathologists. The changing epidemiology of HIV infection, a growing appreciation of the duration of clinical latency, the ability to identify asymptomatic infection, and the unequivocal evidence of the occupational transmission of HIV to health care workers have broadened the concern about risks posed by these patients to additional physician groups, particularly pediatricians, surgeons, gynecologists, and obstetricians. A second wave of physician resistance to the care of HIV-infected patients began in the summer of 1987 with the announcement by the Centers for Disease Control of the occupational transmission of HIV by splashed blood in three health care workers[2] and the declaration by Dudley Johnson, MD, a Milwaukee cardiovascular surgeon, that he would not do surgical procedures on any HIV-infected person.[3] For every physician who overtly refuses to care for HIV-infected patients, there are undoubtedly many who are deeply concerned about the personal risk this care may entail and who struggle to balance this risk with a sense of professional and personal responsibility.

The History of Professional Responsibility in Medicine

Physicians wrestling with questions of risk and responsibility commonly turn to the history of medicine for evidence of a professional ethic in practice. In fact, supporters of a universal and constant duty of physicians to treat the sick regardless of personal risk have justified their position by

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CDC = Centers for Disease Control
HIV = human immunodeficiency virus
SFGH = San Francisco General Hospital [Medical Center]

saying "It is what doctors have always done." As Zuger and Miles point out, however, the record does not show a monolithic standard of physician behavior.[4] Commenting on four epidemics between AD 166 and 1793, they note that, on each occasion, physicians abandoned afflicted city dwellers and fled to the countryside to reduce their own risk of infection. Based on these examples of self-interested behavior, the authors conclude that history does not provide an imperative to today's physicians to care for patients regardless of personal risk. Although this conclusion may be warranted on the empiric basis of historical physician behavior, it overlooks a much more unified sense of what the medical profession ought to be doing. The comments of social critics about lapses in care are telling. Of the London plague of 1665, Daniel Defoe wrote, "Great was the reproach thrown on those physicians who left their patients during the sickness, and now they came to town again nobody cared to employ them."[5] By the Philadelphia yellow fever epidemic in 1793, a societal understanding of expected physician behavior was expressed by a newspaper editorialist: "Physicians are justly considered as public property, and like military men it pertains to their profession to be occasionally in the way of danger" ([Philadelphia] *Federal Gazette,* October 2, 1793, p 3).

Medicine has continued to evolve as a profession in the 200 years since the yellow fever epidemic. A consideration of the recurrent outbreaks of cholera in the late 19th century and the poliomyelitis pandemics of the mid-20th century suggests that society at large and the medical profession increasingly hold as an ideal a sense of physicians' obligation to care despite personal risk. Practitioners during the polio pandemic report that a disguised avoidance of afflicted patients was virtually unheard of, much less an overt refusal to care, despite a real risk of transmission of the poliovirus to physicians and their families.

I would argue, therefore, that while the historical record does not show us an unbroken line of physicians caring for ill patients without regard to personal danger, there is a developing consensus both inside and outside the profession that physicians do have a duty to care for the sick in the face of some personal risk. This sense of obligation can be recognized in the comments of physicians who assert it positively and in the expectations of society as articulated by politicians and commentators, but also in the rationalizations of some who deny it.

Categoric and Contractual Models of Physician Obligation

A survey of the history of epidemic disease reveals two concepts of professional obligation that continue to influence our understanding of our responsibilities in the AIDS era. In one formulation, physicians as a group acquire an obligation to society at large by virtue of the profession's subsidized education and privileged position as a protected monopoly. In exchange, society expects that, one, we will adequately regulate ourselves, and, two, we will meet the needs of the sick or, at least, those of the sick who our society wants cared for. It was to this contractual relationship that the Philadelphia editorialist was referring when he spoke of physicians as "public property." This model can be contrasted with a more personal or categoric one in which a duty to each ill person on the part of each physician is seen as inherent in the moral undertaking of medicine. During the Philadelphia epidemic, Benjamin Rush expressed a categoric understanding of professional responsibility by an analogy between a physician's responsibility to ill patients and a wife's duties toward a gravely ill husband. In this model of the relationship between patient and physician, society is an interested bystander rather than a party to a negotiation.

Not surprisingly, the law does not address the nature of medicine as a moral undertaking. Legal obligations for physicians are established within the contractual framework, for the most part, for groups of practitioners rather than for individual physicians.[6,7] Hospitals must provide emergency care to patients, regardless of concurrent medical problems including HIV infection, but the law takes no interest in the internal mechanisms used to accomplish this. From the legal point of view, a system in which one volunteer physician provides all care to HIV-infected persons is as acceptable as one in which all staff in a particular area are required to share equally, so long as emergency care is provided. Other positive obligations affecting hospitals include the duty of institutions of "last resort" to provide a full range of services to their constituent populations; a pertinent example is the obligation of public hospitals to provide comprehensive and appropriate care including indicated elective operations to the community's indigent patients, regardless of HIV status. Finally, institutions receiving federal financial support may not discriminate in the provision of treatment and are required to care for HIV-infected persons. The obligations to individual patients established in law and bearing on individual physicians are relatively minimal. Physicians must treat any patient presenting with a true emergency condition and may not abruptly and unilaterally terminate a patient care relationship without providing notice and an adequate opportunity for the patient to make alternative arrangements for care. Thus, except for an emergency presentation, individual physicians are at liberty in their offices to accept or decline HIV-infected patients, just as they may accept or decline Medicaid patients.

Professional organizations have looked at this question of physician responsibility differently. The American Board of Internal Medicine issued a statement in the fall of 1988 in which it took a categoric position:

> The American Board of Internal Medicine considers it unethical for a physician to refuse to treat a patient solely on the basis of that patient's disease when the disease is within the physician's area of competence. This has particular relevance to patients with the acquired immunodeficiency syndrome or human immunodeficiency virus seropositivity.[8]

In a similar statement, the American College of Physicians asserted, "The denial of appropriate care to patients for any reason is unethical."[9] The Association of American Medical Colleges articulated a categoric formulation of professional responsibility in a statement that had special pertinence for training programs:

> Medical students, residents and faculty have a fundamental responsibility to provide care for all patients assigned to them, regardless of diagnosis. A failure to accept this responsibility violates a basic tenet of the medical

profession—to place the patient's interest and welfare first. Faculty members have a special responsibility to model the professional behavior and attitudes expected of physicians in training in their own willingness to provide competent, sensitive, and compassionate care to all patients.[10]

The American Medical Association has taken a more contractual position on the question of physicians' responsibility to care for HIV-infected patients, consistent with its vigorous contention that individual physicians are at liberty to decline to care for any person they choose, except for patients presenting with an emergency condition.[11]

It is important to recognize that the contractual and categoric formulations of professional obligation coexist in medicine today, and both inform the discussion of physicians' obligations to persons infected with HIV. Physicians tend to assume that the professional ethic is monolithic and are often disconcerted to encounter competing understandings of professional responsibility. The existence of two distinct models for physicians' duty, at times relatively compatible and at other times in conflict, has complicated the development of consensus among physicians. The nursing profession, in contrast, has a predominantly categoric understanding of professional obligation.[12]

Many people understand the categoric concept of professional duty to demand care under all circumstances, in contrast to the contractual approach that permits physicians to decline relationships with patients at their discretion. A closer look suggests that the categoric formulation of professional obligation does accommodate physicians' discretion. As John Arras points out, however, in the categoric framework, "the reasons for declining to care are not of moral indifference."[13] Refusing to care for someone because that person does not have enough money to pay for an office visit, refusing to care on the basis of racial or religious prejudice, and refusing to care for someone because that care poses an extreme risk to providers are morally different decisions, although the outcome may be the same from a patient's standpoint. An example of the effect of risk to physicians on patient management makes this clear. A belligerent, intoxicated patient came to an emergency department for evaluation of a subcutaneous cyst. When the physician approached him, the patient offered to "knock out all your teeth." The physician considered this to be more than an idle threat, weighed the gravity of the presenting complaint, and told the patient to leave the department and to return for an evaluation when he was more sober and cooperative. Most physicians would not think that this physician abdicated her responsibility to the patient. The particulars that make her decision acceptable are the semiobjective nature of the risk posed by the patient and the relationship between the reduction in risk to the care provider and the loss of benefit to the patient. In the case at hand, any reasonable person viewing the situation in the examining room would likely have had a sense of real physical threat. An idiosyncratic refusal to care for patients on the basis of a highly personal perception of risk is less acceptable than declining to care for a patient whose management entails assuming risks that are generally recognized as extreme.[14] In addition, in the example, the loss of benefit to the patient as a result of deferring treatment was trivial. The potential for a substantial loss of benefit to the patient increases the physician's obligation to treat; it is for this reason that care providers in emergency departments are from time to time assaulted by patients who are being evaluated for conditions such as encephalopathy, meningitis, and sepsis.

Understanding the Tensions Over Professional Responsibility at SFGH

For the past two years, under increasing public scrutiny, physicians at San Francisco General Hospital Medical Center have debated their responsibility to HIV-infected patients. Widespread discussion that began with the report by the Centers for Disease Control (CDC) of three cases of apparent occupational transmission by splash exposure[2] was greatly intensified by the announcement in October 1987 of an occupational seroconversion in an SFGH health care worker. Lorraine Day, MD, until her resignation as the Chief of Orthopedic Surgery, had been most identified with the position that the care of HIV-infected persons is extremely dangerous and that physicians should not be required to provide it (C. Pogash, "Bad Blood," *San Francisco Chronicle-Examiner,* January 15, 1989 [Image Magazine], pp 4-8; Columbia Broadcasting System, *60 Minutes,* September 24, 1989). The tensions within SFGH have arisen from three sources: the competing concepts of professional duty, the heterogeneity of exposure to potentially infective fluids and sharp instruments, and the pronounced variation in the perceived risk of occupational transmission.

The coexistence and competition within the hospital of the contractual and categoric models can be seen in the response of the two main clinical services to a charge from hospital administration. Early in the epidemic, the chief administrative officer of SFGH reaffirmed the hospital's commitment, mandated by law, to provide services to patients, particularly the county's indigent, regardless of HIV status. He then delegated to the services that are within the purview of each department. The main clinical departments reacted differently to that charge. The chief of surgery, working from a contractual formulation, guaranteed the provision of needed surgical services but permitted the shifting of elective surgical patients from reluctant staff surgeons to the care of willing colleagues. For logistic reasons, discretionary patient shifting was not available to surgical house staff. Reflecting a categoric understanding of physician duties, the chief of medicine asserted his expectation that each health care provider in the department would care for patients, regardless of HIV status. (In contrast to the surgery department, many faculty in the department of medicine have minimal patient contact and so were essentially unaffected by this standard.)

From a patient's point of view, the difference in understanding of professional obligation in the two major clinical departments has not been particularly important. In the large surgical units, there have been enough surgeons willing to operate on HIV-infected patients to permit uninterrupted care with or without patient shifting. In the smaller services with one or two surgeons, the contractual model has been problematic because it legitimizes patient shifting at the discretion of apprehensive or reluctant physicians, in the absence of providers willing to accept care. Individual physicians were obliged to care for HIV-infected patients to discharge the hospital's commitment to its patients. The two concepts of professional obligation have led to conflict between the departments, as members of the department of medicine have pressured those of the department of surgery for a strong categoric statement out of a sense that it is ethically preferable and would improve the access of HIV-infected patients to the services provided by smaller surgical

divisions. The institutionalization of a contractual model has been resisted by the hospital administration as well because it is seen as providing a degree of choice to staff physicians that is not feasible for other personnel at risk, including nurses and phlebotomists.

A second element in the tension between medicine and surgery is the obvious heterogeneity in exposure to infective fluids and sharp instruments. Differences in exposure to infective fluids and in perceived risk interact in a complicated way; it is often difficult to tell where epidemiologic factors end and psychological ones begin. Common sense and the epidemiology of hepatitis B suggest that, if the prevalence of HIV seropositivity is the same in two physicians' practices, the surgeon will be at greater risk than the internist. On the other hand, the assumption of equal prevalence is unlikely to be accurate because HIV-infected persons have primarily medical rather than surgical illnesses. It is worth noting that among documented cases of occupational transmission, nurses and clinical laboratory personnel have outnumbered physicians of any specialty.

The third element feeding the tension is the nonepidemiologic variation in the perception of risk. Surgeons perceive themselves to be at a much higher risk than internists and argue that their impression reflects their exposure to blood and sharp instruments. We know, however, that a perception of risk is strongly affected by factors that have nothing to do with the probability of occupational transmission. These include the risk behavior of the patient, the sex of the physician when the predominant AIDS risk behavior is homosexuality or bisexuality, the clinical status of the patient—demented patients and those with visible lesions of Kaposi's sarcoma are perceived as more dangerous (M. Grade, UCSF AIDS Prevention Education Projects, oral communication, September 1988)—physician homophobia, prejudicial attitudes on the part of a physician, death anxiety and other psychological characteristics, and physician specialty. Many of these are likely to be interrelated; they may operate singly or in combination to produce large differences in the degree of risk perceived by two persons analyzing the same epidemiologic situation. As it happens, many of the factors that intensify a perception of risk are present in a greater degree in surgeons than in internists[15]; it is difficult to separate the component of concern resulting from intense exposure to blood and sharp instruments from this nonepidemiologic component.

These different assessments of risk would be nothing but psychological curiosities were it not for the problem of working out the relationships between risk and responsibility within the categoric model. As the emergency department example showed, refusing to care for an ill patient is justifiable only when the postulated hazard is a clear and present danger, apparent to other reasonable observers, and when the patient's loss of benefit does not grossly exceed the provider's increased safety. Markedly divergent assessments of risk, reflecting both heterogeneity in exposure and the numerous psychological issues that influence perceptions of risk, have hampered negotiations among colleagues over modifications of surgical procedures. Many surgeons have felt themselves to be in great danger; because of the magnitude of the hazard they perceive, substantial modifications in care, including nonsurgical treatment such as prolonged traction instead of open reduction and internal fixation for fractures, have seemed justified to them. Internists have characteristically responded to these experimental risk assessments by citing epidemiologic data emphasizing the rarity of seropositivity in health care workers with extensive contact with infected patients and noting the frequency with which seropositivity in health care workers can be explained by recognized risk behaviors. In some cases, this attempt to use CDC data to reduce anxiety has not been successful. It instead appears to have fostered suspicion and hostility toward the CDC and other infection control authorities.

The Tension Between Risk and Responsibility—Moving the Discussion Forward

Competing concepts of professional responsibility have existed within medicine for hundreds of years; in this area, as in others, the HIV epidemic is reminding us of an old problem that we are unlikely to resolve in the near term. In addition to the elements described, the current negotiations at SFGH have been hampered by a tendency to focus on procedural aspects of HIV testing and the enthusiasm of the news media for presenting the conflict as a struggle between powerful hospital personalities. Although it is unclear whether preoperative testing actually increases the safety of health care workers in the surgery department, most infection control authorities have little resistance to preoperative HIV screening per se. The issue became contentious because of a suspicion that, having found a patient preoperatively to be seropositive, some surgeons would select a less effective, modified operation or nonsurgical approaches without participating in an explicit discussion of the choices being made. In an effort to prevent a covert denial of surgical care, access to preoperative HIV antibody testing has been restricted in many hospitals. This strategy shifted the focus of discussion away from more important and fundamental questions. At San Francisco General Hospital, HIV antibody testing is available at the discretion of treating physicians; the adequacy of informed consent and the quality of counseling before and after testing remain under close scrutiny. The degree of oversight and even the requirement for informed consent, stipulated by law in California, are regarded by some physicians as intrusions into professional autonomy.

The preference of many journalists for understanding and presenting the complex issues involved in weighing professional risk and responsibility as personality conflicts, a sort of medical mud wrestling, has been counterproductive as well. In addition to trivializing important ethical issues, media attention has encouraged grandstanding and ad hominem argument and made it difficult for protagonists to return to the hospital and participate productively in medical staff negotiations over these difficult problems.

The process by which physicians will develop a consensus on the management of HIV-infected patients is one of thoughtful discussion, empathic attention to the working conditions and apprehensions of colleagues, and negotiation within the limits established by legal obligations, institutional philosophy, and professional ethics. Hospitals, medical schools, and professional organizations can assist this discussion by providing clear statements of organizational expectations. At SFGH, the hospital bylaws have been rewritten to emphasize the obligation of every staff physician to provide the highest standard of care to all patients, regardless of infectious disease status. Medical institutions can also support health care workers by ensuring adequate training and material support for infection control and providing in-

surance opportunities to all health care workers and appropriate psychological support and opportunities for restorative recreation. The stakes are high. The profession runs the risk of confirming the suspicions of many critics that health care has become a commercial enterprise with service to the suffering as an occasional by-product. We must recognize the significance of physicians' negotiations over risk and responsibility in the HIV epidemic to the ill persons who prompted it and to the medical profession.

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Epitomes

Important Advances in Clinical Medicine

Radiology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in radiology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in radiology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Radiology of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Color Doppler Ultrasonography of the Liver

Color Doppler ultrasonography (CDU) is a relatively new technique in which color-coded images of flowing blood are superimposed on a gray-scale sonogram. The images thus obtained simultaneously display both physiologic and anatomic information in real time. Until recently, the use of CDU was limited to the superficial circulation, such as the carotid arteries, deep veins of the leg, and dialysis access grafts. Advancements in the ultrasound technology, however, now enable the use of CDU to investigate the abdominal vasculature as well. Our initial experience with this technique in evaluating the liver has been encouraging. With CDU the hepatic artery, portal vein, and the hepatic veins can be displayed, providing unique information noninvasively.

The hepatic artery can be completely occluded in the liver with little or no major consequences. In fact, about the only notable abnormality to affect the hepatic artery is pseudoaneurysm. Color Doppler ultrasonography yields dramatic images of pseudoaneurysms and should be diagnostic. In a transplanted liver, on the other hand, hepatic artery flow is essential, and Doppler ultrasonography is the method of choice for determining patency. Although conventional duplex ultrasonography will suffice, CDU decreases the scan time considerably. It is of particular help in pediatric transplant patients in whom the minute hepatic artery can be particularly challenging to locate.

Portal vein flow is affected by most common forms of chronic liver disease that lead to cirrhosis and portal hypertension. Color Doppler imaging can depict the portal venous system readily in almost all patients and definitively determine flow direction. Thrombosis, varices, and other portal vein abnormalities are readily evaluated noninvasively using CDU. Our experience with this technique in portosystemic shunts has also been encouraging. We have evaluated 42 shunts and have found the technique to be accurate in establishing patency.

Color Doppler ultrasonography is also an excellent method for evaluating the hepatic veins. The Budd-Chiari syndrome, or hepatic veno-occlusive disease, is relatively unusual, but the symptoms are sufficiently nonspecific that a noninvasive screening procedure would be of considerable value. In our preliminary study of the use of CDU in patients with the Budd-Chiari syndrome, we found excellent correlation when it was compared with other imaging procedures and venography. The patency of individual veins could be established definitively, as could sites of occlusion. Reversal of hepatic vein flow and the identification of intrahepatic collaterals were pathognomonic of the Budd-Chiari syndrome. Color Doppler imaging also facilitated the evaluation of the inferior vena cava and could be used postoperatively in this group of patients to evaluate mesoatrial shunts.

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Endovaginal Ultrasonography

Endovaginal sonography, initially used chiefly for in vitro fertilization, has recently seen widespread application in pelvic ultrasonography. The traditional transabdominal approach to pelvic ultrasonography requires a distended urinary bladder to permit visualization of the pelvic organs. In contrast, endovaginal ultrasonography uses a transducer inserted into the vagina and is done with the bladder completely empty. Because of the proximity of the transducer to the region of interest, higher scanning frequencies (typically 5 MHz or greater) can be used, thereby increasing resolution. Endovaginal ultrasonographic transducers may be obtained for most brands of ultrasound equipment. The procedure is generally not painful, and patient acceptance is high. Endovaginal ultrasonography may be contraindicated in women who have not been sexually active or those who have had vaginal surgical procedures.

The usefulness of endovaginal ultrasonography is most apparent in the evaluation of patients with complicated intrauterine pregnancy or suspected ectopic gestation. A definitive diagnosis of intrauterine pregnancy can be made one to two weeks earlier than with the transabdominal method. Embryonic cardiac activity can be readily identified with endo-

vaginal ultrasonography, permitting a confirmation of viability. This technique also permits direct visualization of ectopic pregnancies in many cases, allowing patients to go directly to laparotomy without the need for other diagnostic procedures.

The procedure is equally capable of detecting and characterizing disease involving the uterus, adnexa, and surrounding structures. Small ovarian masses and uterine leiomyomas can be shown. Fallopian tube dilatation, which usually has a nonspecific appearance on transabdominal ultrasonography, can be specifically diagnosed using the endovaginal method.

Despite the advantages of the procedure, most investigators continue to use it as an adjunct to transabdominal ultrasonography. In one prospective study comparing the two techniques, however, endovaginal ultrasonography provided more information in 65 of 108 nonpregnant patients and was judged inferior in only 4 instances. It was concluded that the endovaginal method could become the initial approach for routine pelvic sonography, with the use of the transabdominal approach advocated in selected patients.

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Percutaneous Cholecystostomy for Acute Cholecystitis

CHOLECYSTECTOMY is the accepted method of treating patients with acute cholecystitis. Because emergency cholecystectomy for acute cholecystitis is associated with a higher mortality rate than an elective procedure, some suggest delaying cholecystectomy until a patient is less ill. Cholecystostomy has been advocated to decompress the inflamed gallbladder until the patient's condition allows a definitive cholecystectomy. Recent reports have shown that percutaneous cholecystostomy may be helpful in managing patients admitted to hospital with suspected acute cholecystitis.

Several catheter systems have been developed for percutaneous cholecystostomy. The catheters all have a securing device such as a Cope-type loop to prevent catheter dislodgement from the gallbladder. Although ultrasonography, computed tomography, and fluoroscopy have been used to guide catheter insertion, ultrasonography is the most frequently used method to guide percutaneous cholecystostomy. Its advantage is that the equipment is portable and therefore the entire procedure can be done at a patient's bedside.

The cholecystostomy catheter may be inserted by one person under ultrasonographic guidance. After the gallbladder is located with ultrasonography and using only local anesthesia, the catheter system is placed transhepatically under real-time control into the gallbladder. After the catheter is placed, a specimen of bile is taken for culture and the catheter is positioned for intermittent suction. A fluoroscopy-guided cholangiogram through the catheter is usually not done until 48 hours after catheter insertion.

Reports of percutaneous cholecystostomy have shown that major complications, such as catheter dislodgement or hemorrhage, are few, the incidence comparing favorably with that of complications from surgical cholecystostomy.

In a few instances of gangrenous cholecystitis, cholecystostomy may not prove helpful and patients will require emergency cholecystectomy. In most circumstances, however, the patient's condition improves after catheter placement, and further treatment, such as a cholecystectomy, can be delayed. In fact, in a large number of patients in hospital, especially those with acute acalculous cholecystitis, percutaneous cholecystostomy has proved to be a definitive treatment, thus completely avoiding cholecystectomy.

Percutaneous cholecystostomy may be a safe and beneficial method to manage patients with suspected acute cholecystitis.

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Gadolinium in Magnetic Resonance Imaging of the Central Nervous System

MAGNETIC RESONANCE IMAGING (MRI) has become an important initial method for the diagnostic imaging of diseases of the central nervous system. Magnetic resonance imaging, however, has difficulty in distinguishing the alteration of the blood-brain barrier of a localized pathologic lesion that may be surrounded by extensive edema. This difficulty has prompted the development of gadolinium-labeled diethylenetriaminepentaacetic acid (Gd-DTPA), known in the United States as gadopentetate dimeglumine (Magnevist). The availability of Gd-DTPA as an approved contrast agent for use in diagnosing central nervous system disorders has revolutionized the capabilities of MRI. It is now possible not only to identify a localized or diffuse disorder with great sensitivity but also to demonstrate the alteration of the blood-brain barrier following the intravenous administration of Gd-DTPA.

A wide variety of both intra-axial and extra-axial tumors are optimally visualized following the administration of Gd-DTPA. Metastatic brain tumors as small as 2 to 3 mm may be shown following Gd-DTPA enhancement. Gd-DTPA-enhanced MRI is now the imaging procedure of choice for patients with possible metastatic disease to the brain or spinal cord. Metastatic disease to the meninges may be difficult to show with conventional x-ray computed tomography because of the Hounsfield artifact problem. This limitation is resolved with MRI. In the presence of meningeal tumor deposits, there is notable enhancement of the dural margins following the administration of Gd-DTPA.

Images of infections of the meninges, either acute or chronic, and parenchymal infections such as an abscess or fungal granuloma usually are enhanced after a Gd-DTPA infusion. Aneurysms and arteriovenous malformations are well shown on conventional MRI scans. Enhancement is variable, depending on the rate of flow through these lesions. High flow regions within arteriovenous malformations or aneurysms will not be enhanced. The visualization of areas of slow flow in venous or cryptic malformations may be improved with contrast enhancement.

Gd-DTPA-enhanced MRI has become the state-of-the-art method of imaging a variety of abnormalities. It has

none of the risks associated with iodinated contrast agents used with x-ray computed tomography. The use of Gd-DTPA solves some of the diagnostic problems associated with unenhanced magnetic resonance scans. It helps characterize brain abnormalities detected on the conventional scans, assists with the separation of tumor from surrounding edema, and increases the sensitivity for detecting a variety of central nervous system lesions.

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Magnetic Resonance Imaging for Diagnosing Avascular Necrosis of Bone

MOST COMMONLY SEEN in the femoral head, bony avascular necrosis may lead to severe pain and disability if allowed to progress. Avascular necrosis appears both unilaterally and bilaterally. Though it may occur in otherwise healthy persons, people with blood dyscrasia or those on long-term steroid therapy are particularly prone to it. In our experience heavy alcohol users may present with obscure hip pain due to avascular necrosis. It may also develop in patients with a malignant neoplasm who are undergoing chemotherapy. In this group the avascular necrosis is sometimes confused with metastatic disease.

An early diagnosis is crucial to the outcome, for the success rate following surgical decompression is considerably better in patients with mild disease than in those in more advanced stages. Recently magnetic resonance imaging (MRI) has proved to be the most sensitive method available for the early diagnosis of femoral avascular necrosis. In 1987 MRI was found to be 100% sensitive and specific as a screening tool among 32 patients on long-term steroid use, superior to both conventional radiography and scintigraphy by a comfortable margin. Three of seven patients with abnormal MRI findings but normal radiographic and bone scan results were pain-free at the time of evaluation. All later had pathologic findings at a surgical procedure or the eventual development of characteristic radiographic changes. Though cost may limit its adoption, MRI has potential as a screening aid in asymptomatic patients at high risk for avascular necrosis.

Magnetic resonance imaging findings in patients with avascular necrosis depend to some degree on the stage of the disease. Always, however, they involve a relative decrease in signal. On T1-weighted images—T1 and T2 referring to the nuclear spin relaxation times—patches of moderately decreased signal may be seen within the marrow space. With T2-weighting on high-field units (1.5 tesla), there may be a "double-line sign" in which a bright strip of high signal intensity appears within an area of decreased signal. The use of both T2- and T1-weighted imaging may increase the sensitivity of MRI in detecting avascular necrosis.

We advocate the use of MRI of the hips in patients who are seen for hip pain and patients who have a predisposition for avascular necrosis.

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Biliary Lithotripsy

BILIARY LITHOTRIPSY or extracorporeal shock-wave lithotripsy (ESWL) for gallbladder stones is an exciting new alternative to standard cholecystectomy. Biliary ESWL may be used to treat stones in the intrahepatic and extrahepatic bile ducts, as well as in the gallbladder. At present these procedures are considered investigational in the United States.

Shock waves may be produced by various means. The spark-gap method uses a spark plug submerged underwater to generate the shock waves. The electromagnetic technique uses an oscillating membrane and a lens, and a third method, the piezoelectric technique, uses piezoceramic crystals. The shock waves emanate from these generators and are focused by a juxtaposed semiellipsoid cup or a lens onto the gallstones. Stones will fragment if the shock-wave energy overcomes the inherent forces of the gallstones.

All ESWL systems are efficacious to varying degrees. The major advantage of the spark-gap method is the power and efficacy of stone fragmentation; the piezoelectric machines are less powerful and commonly require more than one treatment session. The piezoelectric lithotripters cause only minimal patient discomfort, however, and require no analgesia. In most ESWL gallstone protocols in this country, patients are in the hospital for only one night.

The differences between biliary and renal lithotripters include the following: ultrasonography is used for localization rather than fluoroscopy, a water membrane has replaced the water bath, and focusing of the semiellipsoid has been improved, which helps reduce patient discomfort. Currently general or epidural anesthesia is unnecessary for gallstone lithotripsy; epidural anesthesia is used for bile duct ESWL.

In experimental and investigational in vivo studies, biliary ESWL has been relatively safe to date. Mild soft tissue damage in the form of petechiae, hemorrhage, and vascular thrombosis appears to be reversible within a week. Acute injury necessitating cholecystectomy has not been reported.

The success rate of ESWL fragmentation has been more than 90% in most early studies on patients. Only 15% to 30% of patients with symptomatic gallstones qualify for ESWL. Qualification criteria include no more than three stones, no stone greater than 3 cm, the cystic duct must be patent, the patient has symptoms related to gallstone disease, there is no jaundice or evidence of common duct stones, the patient must not be pregnant, there is no aneurysm or cyst in the path of the shock waves, and there must not be evidence of acute cholecystitis or pancreatitis.

The most common side effect of biliary ESWL is transient biliary colic, which occurs by intermittent obstruction and the passage of small fragments through the cystic duct. This occurs in about a third of patients. Other side effects include transient cutaneous petechiae and microscopic hematuria; these are self-limited. Pancreatitis due to stone passage has been extremely uncommon.

The advantages of ESWL include the avoidance of general anesthesia, a major operation, and an abdominal scar.

The recovery time from ESWL is rapid, and patients return to work within days. Because ESWL essentially fragments large stones into smaller fragments, current practice generally includes oral bile salt therapy (ursodeoxycholic acid) in combination with ESWL to dissolve residual fragments. This adjunctive use of bile salt is another reason why the cystic duct must be patent in patients undergoing ESWL—that is, to permit oral bile acids to enter the gallbladder.

This procedure usually costs about ⅔ to ¾ the cost of cholecystectomy in a given institution. The cost of ursodeoxycholic acid therapy must be added to that of ESWL for an overall price, especially if long-term oral bile acid therapy is necessary or for treatment of stone recurrence. Recent data suggest that stone recurrence is at a 5% to 10% annual rate for five years, then declines considerably; this implies about a 50% five-year gallstone recurrence rate.

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Percutaneous Management of Common Bile Duct Calculi

SEVERAL RADIOLOGIC interventional techniques have been devised for the management of common bile duct calculi. These, as well as endoscopic sphincterotomy, offer reasonable alternatives to the more traditional surgical approaches.

Nonimpacted mobile stones less than 2 cm in diameter are most safely removed endoscopically following a sphincterotomy if no T-tube tract is present. For interventional radiologists, percutaneous access to the biliary tree can be gained in one of two ways: percutaneously through a transhepatic route, or by a T-tube or similar tract inserted following cholecystectomy. A T-tube tract that has been in place four to six weeks offers excellent and safe access to the biliary tree. For large or impacted stones, or for stones out of reach of endoscopists, a transhepatic route can be used when no T-tube is present. While most authors report a 7% to 10% serious morbidity and 1% to 3% mortality using a transhepatic catheter, most of the patients studied were compromised by malignant biliary obstruction. For benign stone disease, these rates are much lower.

Various percutaneous methods are available for manipulating stones too large or impacted to immediately remove with a basket. Generally these methods are less cumbersome when done percutaneously than endoscopically, often with the patient fully awake. Most experience is with contact cholesterol solvents, such as the experimental methyl tertiary butyl ether, and monooctanoin, which has been approved by the Food and Drug Administration for common bile duct calculi.

Ether will completely dissolve about 10% of them within 30 minutes and the rest will shrink or soften. Working with ether is tedious; the agent is potentially explosive, its perfusion must be continuously monitored, its fumes eventually permeate the ambient air, and a special occlusion balloon placed percutaneously distal to the stone is necessary to reduce its flow into the duodenum, where its greatest systemic absorption occurs. On the other hand, monooctanoin, a naturally occurring digestion product, can be perfused at the bedside or on an outpatient basis if certain precautions are taken. Nevertheless, even after 12 hours of monooctanoin perfusion, most stones will soften so that fragmentation will occur when crushed in a Dormia basket, and the fragments can be either pushed into the duodenum or removed percutaneously. With patience, either agent or a combination of the two will eventually hasten the complete removal of nearly all biliary calculi with few ill effects.

Other techniques such as mechanical or laser pulverization of common duct calculi have been described to a lesser extent. If percutaneous or endoscopic access to biliary calculi is available, fragmentation of the stones by any method in conjunction with cholesterol solvent perfusion of the exposed cholesterol cores would probably hasten the stones' dissolution or removal. To date, the implications of shockwave lithotripsy in the management of common duct calculi have yet to be fully realized.

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Transrectal Ultrasonography and Biopsy

PROSTATE ULTRASONOGRAPHY began in the early 1970s, but images were suboptimal and the level of diagnostic accuracy was disappointing. The technique of transrectal ultrasonography in which the ultrasound transducer is placed in the rectum directly against the posterior aspect of the prostate permits the use of higher frequency transducers. This advance has dramatically improved image quality and resolution, which in turn has led to encouraging recent results in the detection of prostatic carcinoma.

The normal anatomy of the prostate can be visualized by ultrasonography and separated into three anatomic zones: peripheral, transitional, and central. These three zones have a different predilection for disease. The transitional zone is the area where benign prostatic hypertrophy occurs. The central zone is relatively free of disease and is compressed between the transitional and peripheral zones in benign prostatic hypertrophy. The peripheral zone is where the majority (70% to 80%) of prostatic carcinomatous lesions arise.

There is growing consensus that most lesions caused by prostatic carcinoma have a hypoechoic appearance on ultrasonography. If this holds true, it has great significance in the potential diagnostic accuracy of ultrasonography in the detection of this disorder. Because the major site (70% to 80%) of prostatic carcinoma is in the peripheral zone, hypoechoic lesions are easily visible in this region because of the peripheral zone's even, highly echogenic appearance. This difference in echo texture between the highly echogenic peripheral

zone and the hypoechoic area permits the early detection of prostatic carcinoma even before these lesions become palpable.

Transrectal ultrasonography also is used as a guide for obtaining accurate biopsy specimens of these lesions, thus enabling real-time visualization of the hypoechoic lesions while the biopsy is being done. This increases diagnostic accuracy and confidence. A recent report indicates that transrectal ultrasonography is twice as sensitive as a digital rectal examination in screening for prostate carcinoma. Although these results are encouraging, prostatic ultrasonography is not considered a screening tool and should still be used in conjunction with the digital rectal examination and a determination of the prostate-specific antigen level.

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Magnetic Resonance Imaging for Staging Head and Neck Cancer

ACCURATE RADIOLOGIC STAGING of head and neck cancer is important in planning treatment and assessing prognosis. The ability of magnetic resonance imaging (MRI) to detect adenopathy and to differentiate the subtle differences in soft tissue boundaries, thus detecting the deep extension of tumors into muscle and fascial planes, has revolutionized the imaging of neoplasms in the extracranial head and neck. Magnetic resonance imaging is also superior to computed tomography in noninvasively assessing the vascular involvement of tumors, often circumventing the need for angiographic procedures.

The abundance of fascial planes in the extracranial head and neck provides excellent anatomic details in T1-weighted images not seen on computed tomograms. This superior contrast resolution can be obtained in the axial, coronal, sagittal, or oblique planes. Most neoplasms can be adequately studied on T1-weighted images. T2-weighted images add information both regarding tumor infiltration into muscle and in differentiating between the fluid and soft tissue components in obstructive sinuses. T1-weighted imaging identifies adenopathy most effectively as intermediate signal nodes surrounded by high-signal fat. T2-weighted images are useful in identifying areas of necrosis as areas of high signal. The presence of necrosis indicates a worsened prognosis.

Magnetic resonance imaging cannot separate reactive or inflammatory nodes from neoplastic nodes. It can accurately identify the precise dimension of cervical nodes; those greater than 1 to 1.5 cm have an increased incidence of malignancy. Extranodal tumor extension has a 50% decreased survival rate compared with disease confined to the lymph nodes. Extranodal spread occurs in 23% of nodes of less than 1 cm and in 60% of nodes of less than 3 cm.

Magnetic resonance-guided aspiration cytology is now possible with MRI-compatible needles. Pentetic acid labeled with gadolinium is by and large useful only to assist in defining the intracranial extension of extracranial neoplasms, small intracanalicular acoustic neuromas, and some tongue neoplasms.

Tumors in the nasopharynx and infratemporal fossa and intracranial extension are best imaged by MRI. It is also the method of choice for locating an unknown primary in a patient with an isolated malignant neck node. The presence of a single metastatic node decreases by 50% the life expectancy of persons with head and neck neoplasms. Adenopathy in nasopharyngeal carcinoma is often bilateral and involves the posterior triangle.

T1-weighted axial, coronal, and sagittal images of the larynx provide excellent information concerning infraglottic or supraglottic extension that is deep to the mucosa.

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Editorials

N-of-1 Randomized Trials—Where Do We Stand?

RANDOMIZED CLINICAL TRIALS in individual subjects (N-of-1 RCTs), described in detail elsewhere in this issue by Eric Larson, are old to psychology but new to clinical medicine. Ironically enough, physicians, in comparison to clinical psychologists, are at a considerable advantage in conducting N-of-1 RCTs. Psychologists are usually evaluating behavioral therapies that cannot be masked and are likely to be subject to carryover effects. For physicians, N-of-1 RCTs are generally used to assess drug therapy that often acts, and ceases to act, quickly and for which full double-masking can be undertaken. Nevertheless, psychologists' 30-year experience compares with the less than 3 years in which physicians have been using N-of-1 RCTs in an intensive way. As a result, there are many questions about the technique that remain to be answered.

As described by Larson, N-of-1 RCTs generally consist of a series of pairs of treatment periods, with each pair including one period on active or experimental medication and one period on placebo or alternative. The order of the active and placebo medication within pairs is determined by random allocation. Treatment targets (a laboratory measurement, physical sign, or [most often] patient symptoms) are monitored throughout the trial. Differences between active and placebo periods can be evaluated by intuition, examining graphic representations, or formal statistical analysis.

The first set of questions concerning N-of-1 RCTs that remains to be answered has to do with the optimal method of conducting N-of-1 RCTs. Larson, for instance, suggests that statistical power can be gained by abandoning the usual approach of paired treatment periods and using unconstrained randomization. Using unconstrained randomization permits the possibility of, for instance, six treatment periods being ordered so that the first three all use placebo and the last three use active treatment. Our bias is that when studying individual patients, there is an excessive risk that steady improvement or deterioration, or the occurrence of a single exacerbating or ameliorating event at the point where placebo and an active agent switch, could invalidate the results of a design using unconstrained randomization. Experience using both approaches will, however, be required to determine whether or not our concerns are justified.

A second methodologic issue concerns the statistical analysis of N-of-1 RCTs. Larson refers only to nonparametric methods. These are limited in that they do not take into account the magnitude of differences between active and placebo periods in determining how likely the results were to have occurred by chance. We think that more powerful conventional parametric techniques can be applied to the analysis of N-of-1 RCTs.[1] Other practical issues in doing N-of-1 RCTs include the best way of measuring symptoms, the interpretation of symptom measurement,[2] the optimal trade-off between the length and the number of treatment periods, and the importance of statistical analysis in interpreting the results. While we have our opinions on these issues,[1] they will ideally be explored by investigators interested in N-of-1 methodology.

A second set of questions concerning N-of-1 RCTs has to do with how practical and useful they will prove in clinical practice. Larson reports our initial experience with 42 N-of-1 RCTs. Subsequent trials have continued to demonstrate the ability of the method to resolve difficult clinical dilemmas and the fact that, based on the results, treatment frequently changes.[3] This does not establish, however, whether physicians will continue to rely on open, unmasked, before and after studies, the usual way of conducting clinical practice. While traditional approaches have all the limitations that Larson points out, they have one major advantage: they are easy. N-of-1 RCTs require additional time, effort, and thought that a busy clinician may be reluctant to invest. We have received many inquiries about N-of-1 RCTs but few reports back as to how successful individual experiments, or plans for N-of-1 services, have been. Our results with the technique show that N-of-1 RCTs can result in a more appropriate use of medication and improved clinical care[3]; it will be intriguing to see the extent to which widespread application of the approach occurs.

A final set of questions concerning N-of-1 RCTs has to do with their application in the investigative, rather than the clinical practice, setting, particularly in the development of new drugs. Currently the drug development process is characterized by the commencement of large-scale randomized trials at a point where crucial questions remain unanswered. These include the likely magnitude of the treatment effect, the optimal dose of the medication, the most responsive subgroup(s), and the extent of the heterogeneity of treatment response. A small series of N-of-1 RCTs could be extremely useful in resolving these issues and lead to a much more efficient drug development process. We are currently exploring this question in the testing of a new nootropic agent for senile dementia and are trying to interest other pharmaceutical companies in the use of N-of-1 RCTs.

In these efforts, we have seldom been so bold as to suggest that N-of-1 RCTs could be used in the definitive phases of new drug testing. When we have, the suggestion has been viewed with (perhaps appropriate) skepticism, but we think it is worthy of consideration. Conventional RCTs tell us the average magnitude of an effect in a population. Clinicians treat individual patients, however, not populations. A large series of N-of-1 RCTs could tell a clinician about the number of patients who are likely to respond, the common magnitude of the response, the heterogeneity of the response, and the patient characteristics that predict response. These questions are of primary interest to clinicians. While we do not deny that conventional parallel group RCTs can elucidate these issues to some extent, a large series of N-of-1 RCTs would do better.

The N-of-1 RCTs approach that Larson describes has tremendous potential. We will likely see, in the next decade, the extent to which this potential is realized.

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Are Vitamin A Supplements Needed During Pregnancy?

THE INTRODUCTION of therapeutic retinoids in the 1980s for the treatment of severe acne and psoriasis led to initial claims that these were "miracle" drugs. Within several years of their approval for marketing, however, it became clear that these retinoids posed an unusually high risk for adverse outcomes of pregnancy when taken after conception. The unusual magnitude of this teratogenic risk, coupled with the fact that vitamin A (retinol) was known to induce identical malformations in an experimental setting, has prompted reasonable concerns that supplementation with retinol during pregnancy may be hazardous to developing embryos and fetuses.

This concern will be heightened if experimental studies find that the teratogenic properties of retinol are largely mediated by its metabolic conversion to retinoic acid. This has not been conclusively demonstrated yet, and it is unclear whether retinol induces malformations independently.[1] There are several important pharmacokinetic differences between retinol and retinoic acid that probably act to reduce the potential for human retinol teratogenicity.[2] First, the intake of retinol, in contrast to that of retinoic acid, is necessary for human health, and so a sophisticated system has evolved to maintain body storage and to regulate the serum concentration available to other tissues. Retinol is stored in liver cells and is bound in serum by a specific carrier protein, retinol-binding protein. Excess absorbed retinol is rapidly removed from the serum and stored. Retinoic acid, on the other hand, is not stored and is nonspecifically bound to serum albumin. These different properties make it less likely that excess vitamin A intake might be teratogenic compared with retinoic acid. It is unknown whether excess retinol intake might substantially increase serum levels of all-*trans*-retinoic acid.

Although concerns about the possible teratogenicity of vitamin A are reasonable, there are no systematically conducted human studies to quantitate this risk. Werler recently found a twofold increased risk for vitamin A supplementation and malformation of structures that are composed, at least in part, from cranial neural crest cells.[3] This cell population has been shown to be susceptible to retinoic acid exposure in utero. Werler's study found that 0.2% of control mothers took a vitamin A supplement during early pregnancy. Other surveys have shown geographic variations in vitamin A supplementation but generally have found that less than 0.5% of nonpregnant women of reproductive age take vitamin A supplements of 25,000 IU per day or more. Given this low frequency of supplementation, it will be difficult to identify small increased risks for major malformations in human studies.

The recommendations of Kizer and associates and the Teratology Society to limit the maximum amount of vitamin A per unit dose are sensible and should be implemented. I do not agree that an increased need has been found for vitamin A during pregnancy that requires supplementation. Like most of the components of vitamin supplements taken during pregnancy, vitamin A has traditionally been included in the supplement without any evidence that the usual dietary intake is inadequate and without any evidence that supplementation in developed countries is beneficial to mother or fetus. In developed countries, there appears to be little or no scientific basis for supplementing pregnant women with retinol or retinyl esters, while there is a small possibility of causing harm. It makes sense that vitamin supplements taken prenatally, if they contain vitamin A at all, ought to include only β-carotene as the source of vitamin A. An argument can easily be made that this logic holds for using β-carotene as the source of vitamin A for all commercially available supplements. Regulatory agencies should work with manufacturers to bring about such changes.

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Health Care—Where Are the Problems and Where Are the Solutions?

THE BASIC PROBLEMS in what we call health care are problems for the patient, the family, and, to a greater or lesser extent, the immediate health care environment of an ill person. The problems are actually problems of illness rather than of health, and the first and most important steps in health care have to be taken where the sick, injured, or emotionally disturbed person is, with the resources for care that are available. This is what health care is all about. Yet there are many who view it differently. They see it more as a national problem that, therefore, requires a national solution, by which they mean a nationalized system for rendering patient care. This view is reinforced by the rising cost of health care, which is now nationwide and has become a problem not only for the persons afflicted, their families, and the immediate community, but for business and industry and even for government at the local, state, and national levels. For some time we as a nation have been wont to turn to government when things need to be done that are beyond the reach of individuals or local communities. Government can spread the costs over a wider base, and this substantially reduces personal responsibility for them. The pain of the cost is softened until tax time, and even then it is more often directed toward the amount of the tax, with little consideration of the value of the benefits that in most cases seem to accrue to someone else.

But the fact is the problems of health care and its costs affect almost everyone. They can be viewed as personal, community, local, state, and national problems. For a while there was considerable enthusiasm for a comprehensive, all inclusive program of national health insurance to be administered and paid for by government. As costs have risen, enthusiasm for this has cooled. Actually, a trend quite the opposite has begun to develop. Among the myriads of health care plans and programs that have come into being in business and industry and in government at all levels, there is a notable tendency to push responsibility for paying the costs down-

ward. There is evidence that federal programs are unloading more of their costs onto the states, and, in California at least, the state has started to shift more of the burden down to the counties. The private sector, in similar fashion, has begun to make the beneficiaries participate more directly in the cost of the benefits. This growing decentralization of responsibility and payment for health care costs causes community and personal fiscal pain. It may result in a renewed demand for greater centralization of health care, notwithstanding the evidence that when bureaucratic efforts to control costs are successful, they are done insensitively and at the expense of needed care.

This trend toward decentralization in the long run may be a good thing, however. It could be that the present day problems of health care can be better solved from the bottom up, relying more on local sensitivity and control, rather than depending too much on decisions and choices that are made remote from the real problems of patient care. It would seem more reasonable to look for solutions at the local and perhaps regional level. Americans are pretty good at solving their own problems when they recognize a need. They can be truly innovative in developing available resources to meet their perceived needs. Dollars are part of the problem in health care. Perhaps it is time for health care dollars, collected in taxes and insurance premiums, to flow more freely to where the needs and problems of access, quality, and cost of care are the real, everyday problems of those directly concerned, giving local options more of a chance.

In this connection, we should not forget that no matter how health care is managed or where it is managed, there will never be enough dollars—the demands and expectations will always exceed what can be done with the available resources. Somewhere, hard choices have to be made. It would seem that this could be done more fairly at the local level. Someone has pointed out that there is precedent for Americans making hard choices at the local level. In earlier times this occurred at town meetings. More recently, during World War II, local boards administered a draft law where hard choices had to be made about who would have to offer his life for family, community, and country. This was done by a lottery, with review by a local draft board. There was reasonable fairness. Perhaps something like a health care number and a local health care board could be developed as a means to help make some of the hard decisions fairly and at the local level as to who is to get what in the way of expensive care that is needed but is beyond the basic services that can be afforded for everyone. The inescapable fact remains: the most important and fundamental problems in health care are the problems of providing care at the local level. It is here where the national solutions ought to be found, and it is here where the American system, given a chance, can be at its best.

MSMW

Case Reports

Neonatal Cardiac Allotransplantation Facilitated by In Utero Diagnosis of Hypoplastic Left-Sided Heart Syndrome

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With recent improvements in fetal echocardiography, an accurate diagnosis of congenital heart disease before birth is now feasible. Several reports dating from 1983 conclude that with prenatal diagnosis, rapid and specific postnatal intervention may improve survival.[1-8] We report a case of a neonate with the hypoplastic left-sided heart syndrome diagnosed in utero who received a cardiac allograft at 3 hours of age after cesarean delivery at 37 weeks' gestation. We believe this is the youngest transplant recipient reported to date in the literature.

Report of a Case

In Utero Diagnosis

A 35-year-old woman, gravida 3 para 1, underwent fetal echocardiography at 18 weeks' gestation because of a family history of cardiac disease. A second study at 24 weeks' gestation showed cardiac asymmetry with the following findings: an enlarged and hypertrophied right ventricle, an atretic mitral valve, and a severely hypoplastic left ventricle leading to a small and hypoplastic ascending aorta and aortic arch. The hypoplastic left-sided heart syndrome was confirmed by a third fetal echocardiogram at 27 weeks' gestation. An amniocentesis at 29 weeks revealed a normal 46 XY karyotype. Fetal blood sampling to determine blood type was not done at this time as treatment options had not been delineated. The diagnosis was explained to the family and a referral made to Loma Linda University Medical Center (LLUMC).

Preoperative Evaluation

The parents consulted with the multidisciplinary heart transplant team. Fetal echocardiography at LLUMC during the 35th week of gestation confirmed the diagnosis of a hypoplastic left-sided heart syndrome (Figure 1). The following options were outlined: no intervention, a palliative Norwood procedure,[9] or cardiac transplantation.[10,11] After extensive discussion and consideration, the parents chose to attempt heart transplantation.

The mother had previously undergone a uterine cornual resection with a tubal pregnancy, hence was not a candidate for labor and vaginal delivery. Obstetric sonography showed findings consistent with 36 weeks' gestation with an estimated weight of 3.0 kg. The fetus was registered as a possible recipient for an "O" (universal) donor as his blood type was unknown.

A potential donor was identified soon after registration, and the recipient family was transported to LLUMC in preparation for delivery. The donor was a 2-day-old 2.7-kg anencephalic neonate who showed cessation of brain-stem function, including an absence of respiratory effort after appropriate carbon dioxide stimulation. The blood type was O, Rh positive.

Delivery and Heart Transplantation

With a donor heart waiting and the recipient fetus at 37 weeks' gestation, fetal pulmonary maturity studies of amniotic fluid were not done. A low-segment transverse cesarean section was done without complication using epidural anesthesia, and a 2.9-kg male neonate was delivered. One- and five-minute Apgar scores were 8 and 8, respectively. The umbilical cord blood arterial pH was 7.31, and the venous pH was 7.39.

The infant's condition deteriorated rapidly, with an arterial blood gas measurement showing a pH of 6.96 and a base deficit of −16 ten minutes after birth. Mechanical ventilation was begun with the concentration of inspired oxygen at 40%. Treatment with increased peak inspiratory and positive end-expiratory pressures improved the pH to 7.30, but the partial oxygen pressure remained at 16 torr. The findings of a chest roentgenogram were consistent with retained lung fluid.

Peripheral perfusion was poor. A striking left leg pallor developed, and there was intermittent mottling of the upper extremities. After umbilical venous and arterial lines were placed, infusions of prostaglandin E_1, cyclosporine, antibiotics, and steroids were started. The left leg pallor cleared with the prostaglandin infusion. Postnatal echocardiography confirmed a hypoplastic left-sided heart syndrome, with the foramen ovale marginally patent. The clinical picture was consistent with insufficient peripheral perfusion complicated by restrictive intra-atrial mixing.

Within three hours of birth, the newborn was taken to the operative department where orthotopic heart allotransplantation was done using general anesthesia, extracorporeal circulation, and profound hypothermic circulatory arrest. The donor heart recovery was accomplished in an adjacent surgery. The total cold ischemic time for the donor heart was 95 minutes. The baby left the operating room with stable hemodynamics, a good urine output, and a regular sinus rhythm.

Postoperative Course

The newborn's neurologic recovery was rapid. His respiratory recovery was complicated by increased pulmonary vascular resistance treated with 100% inspired oxygen. Inotropic support was provided using an infusion of dopamine hydrochloride, dobutamine hydrochloride, and isoproterenol hydrochloride. Peritoneal dialysis was required for the first four postoperative days because of impaired renal function. The endotracheal tube was removed on the seventh postoperative day. On the 35th postoperative day, the baby was dis-

(Johnston J, Sakala EP, The Loma Linda University Heart Transplant Group: Neonatal cardiac allotransplantation facilitated by in utero diagnosis of hypoplastic left-sided heart syndrome. West J Med 1990 Jan; 152: 70-72)

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charged from the hospital on a regimen of cyclosporine and azathioprine.

He was treated briefly on three occasions with oral prednisone regimens for presumed rejection early in his postoperative course. He has received no corticosteroid therapy beyond 6 weeks of age. At the time of manuscript preparation, 22 months after the transplant, the infant appears to be developing and growing normally.

Discussion

Since November 1985, 46 babies (younger than 6 months) with the hypoplastic left-sided heart syndrome or other uncorrectable heart disease have undergone cardiac allotransplantation at LLUMC. Of these infants, 41 are surviving with essentially normal growth and development at 1 to 44 months after the transplant. Reasonable results have also been obtained with staged surgical palliation (the Norwood operation). The encouraging outcome of these surgical options challenges the more traditional approach of "letting nature take its course," with the death of these babies being the inevitable end point.

In Utero Diagnosis

The primary issue raised by this case focuses on the potential advantages and disadvantages of the in utero diagnosis of a hypoplastic left-sided heart syndrome and other severe or lethal congenital heart disease (Table 1).

Prenatal counseling. When the diagnosis is made postnatally with the stress of a deteriorating newborn baby overwhelming the parents, a discussion of management options is less than optimal. The pressure of having to make a major decision at a time of high anxiety can lead to parental misunderstanding and frustration. While a prenatal diagnosis may prolong the duration of uncertainty, decisions regarding postnatal management can take place in an environment of organization and thoroughness.

Time for family relocation. An early diagnosis affords time for relocation and reorganization of family life if the option of heart transplantation is chosen. To facilitate follow-up care during the time when rejection of the new heart is most likely, the family must plan to live in close proximity to the transplant center for as long as six months after the transplant. In utero diagnosis allows time to make this transition before the concerns of newborn transplant surgery are placed on the family.

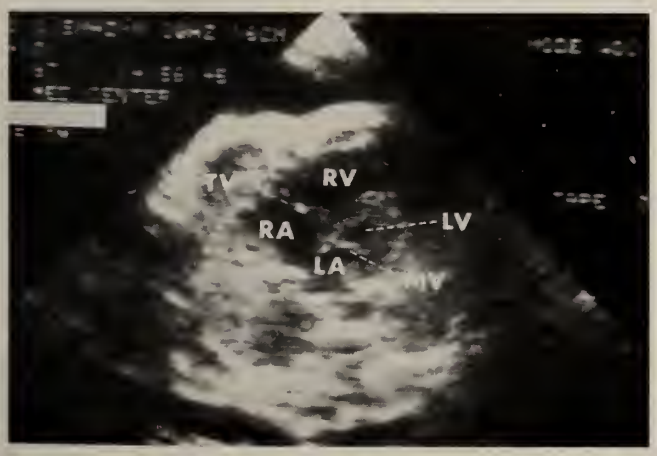

Figure 1.—A fetal echocardiogram with a 4-chamber view of the heart at a gestational age of 35 weeks shows a hypoplastic left ventricle **(LV)** with mitral atresia and an enlarged right ventricle **(RV)**. LA = left atrium, MV = mitral valve, RA = right atrium, TV = tricuspid valve

TABLE 1.—*Possible Advantages and Disadvantages of In Utero Diagnosis*

Advantages
Prenatal counseling regarding management options
Time for relocating family
Additional time for donor search
Allows time for planned delivery in well-equipped facility
Eliminates delay in definitive diagnosis and treatment
Disadvantages
Risk of misdiagnosis
Prolonged emotional distress
Prematurity may lead to a difficult early postoperative course

Time for a donor search. If a diagnosis is made in utero, additional time is gained for finding a suitable donor. Heart transplantation as a therapeutic option is currently limited by the paucity of donor organs. Since November 1985 at LLUMC, about 30% of infants registered for transplantation have died awaiting a replacement organ. Prenatal diagnosis allows the search for a donor heart to be carried out while the recipient fetus remains stable in utero. During this time a fetal chromosomal evaluation can be done to rule out major karyotypic abnormalities. Donor-recipient matching requires a knowledge of blood type and weight limits. Although not carried out in our case, Vincent and co-workers suggest fetal blood sampling for donor matching purposes.[12]

Timed delivery. When an appropriate donor is found, the mother can be transported to the transplant center where a planned delivery of the recipient fetus can take place. If the recipient fetus is at or near term, labor can be induced if the condition of the mother's cervix is favorable. Babies with the hypoplastic left-sided heart syndrome generally have no difficulty coping with the stress of labor. If labor is contraindicated or the cervical condition is unfavorable, a cesarean delivery may be appropriate as in our case. Careful clinical judgment must be exercised if a donor becomes available before the recipient fetus achieves pulmonary maturity. The risks of not using an available donor heart must be balanced with the potential of postoperative respiratory distress due to pulmonary immaturity.

Diagnosis and treatment expedited. An accurate in utero diagnosis can eliminate the frequent delay in definitive diagnosis of congenital heart disease when various other pathologic disorders, such as pulmonary hypertension, sepsis, and severe pneumonia, are being ruled out. Huhta and associates described a case of in utero diagnosis of critical aortic stenosis.[13] The neonate underwent a successful emergency aortic valvotomy at 12 hours of age. In the case of the Loma Linda baby, the rapidity of his deterioration after birth probably would have resulted in his death had not the diagnosis been made antenatally and his mother transferred to the transplant center. Conversely, an incorrect or hasty prenatal diagnosis rendered by inexperienced fetal echocardiographers can lead to unnecessary transport of mothers to transplant centers and needlessly compound parental anxiety.

Anencephalic Donors

Babies born with anencephaly have been considered as possible solid organ donors because of the absence of the cerebral cortex, the lethal nature of the defect, and because

other visceral organs are usually structurally normal. An anencephalic newborn provided the donor heart in our case.

Brain death in the anencephalic baby was determined using criteria described by Ashwal and Schneider[14-16]: coma, an absence of sustained spontaneous respiration when the arterial carbon dioxide pressure is greater than 60 torr, pupils fixed and dilated, an absent oculocephalic reflex (doll's eyes), absent gag and corneal reflexes, normothermia, no use of narcotics, and the blood barbiturate concentration is below therapeutic values.

The successful use of an anencephalic neonate's organ has led to both hopes and concerns about these babies as possible donor sources.[17-20] National attention has been captured as the profound moral, ethical, and legal dimensions of this controversial issue have been reexamined from opposing perspectives.

Prompted by parental request, Loma Linda University Medical Center implemented a protocol devised to study the possibility of organ procurement from anencephalic newborns.[21] The study protocol called for placing an anencephalic newborn on a respirator for a maximum of a week while observing for the occurrence of brain death. Although 12 infants were evaluated over a period of nine months, no successful solid organ donations were realized, and the protocol was abandoned.[22]

Conclusion

Our experience with in utero diagnosis of the hypoplastic left-sided heart syndrome and subsequent transplantation is limited to this single case, the significance of which remains to be established in a larger series. This case shows, however, that it is possible for the in utero diagnosis of the syndrome to improve the chances of locating an appropriate donor. Furthermore, it is possible to successfully transplant a heart into a newborn a few hours after birth.

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Carcinoid Tumors of the Thymus

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When Rosai and Higa first described carcinoid tumors of the thymus, they differentiated them from the more commonly occurring thymomas[1] and defined their association with Cushing's syndrome and multiple endocrine neoplasia.[1,2] We report the cases of six patients with carcinoid tumors of the thymus treated at The University of Texas MD Anderson Cancer Center (Houston) between 1950 and 1988, including their natural history, clinical presentation, endocrine manifestations, and response to therapy.

Report of Cases

Case 1

The patient, a 20-year-old man, was referred to MD Anderson Cancer Center for evaluation of recurrent Cushing's syndrome two years after he began having central obesity and proximal muscle weakness. A computed tomographic (CT) scan revealed a mass in the anterior mediastinum and enlarged adrenal glands. Partial resection had been undertaken, and pathologic examination had revealed carcinoid tumor of the thymus. Postoperative radiotherapy followed. Symptoms and signs of Cushing's syndrome recurred two years later, and the patient underwent reexploration and partial excision of the carcinoid tumor. Postoperatively, the use of metyrapone controlled the symptoms only partially.

When he was referred to us for evaluation, he had cushingoid signs and symptoms. Laboratory evaluation elicited the following values: an elevated cortisol level of 1.08 μmol per liter (normal, 0.22 to 0.67); adrenocorticotropic hormone (ACTH), 283 and 256 ng per liter (normal, 0 to 70); urinary 17-hydroxysteroids, 436.6 μmol per day (normal, 5 to 25); urinary 17-ketosteroids, 170.27 μmol per day (normal, 20 to 70); and urinary 5-hydroxyindoleacetic acid (5-HIAA), 31.5 μmol per day (normal, 10 to 45). A skeletal survey and bone scan revealed metastases in the sixth thoracic vertebra, both femurs, the pelvis, and the right humerus.

Bilateral adrenalectomy resulted in remission of the Cushing's syndrome, and postoperative chemotherapy consisting of fluorouracil, doxorubicin hydrochloride, and strep-

(Venkatesh S, Samaan NA: Carcinoid tumors of the thymus. West J Med 1990 Jan; 152:72-74)

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ABBREVIATIONS USED IN TEXT

ACTH = adrenocorticotropic hormone
CT = computed tomographic
5-HIAA = 5-hydroxyindoleacetic acid

tozocin significantly reduced the patient's bone pain and partially healed the bony metastases.

Case 2

An anterior mediastinal mass was found in a 38-year-old man on a chest x-ray film taken routinely preceding a herniorrhaphy. When the encapsulated mass was surgically removed, pathologic examination revealed it to be a carcinoid tumor of the thymus. The specimen stained positive with Gremelius stain for neurosecretory granules. Five years later a roentgenogram showed tumor recurrence along with lung and vertebral metastases. A CT scan revealed probable metastasis to the right adrenal gland, and a biopsy examination of the mediastinal mass confirmed recurrence of the carcinoid tumor.

A laboratory evaluation elicited the following normal values: serum calcium, 2.25 mmol per liter; cortisol, 0.23 μmol per liter; ACTH, less than 25 ng per liter; 17-ketosteroids, 27.68 μmol per day; urinary 17-hydroxysteroids, 23.5 μmol per day; urinary 5-HIAA, 12.5 μmol per day; and serum serotonin, 28 pg per ml. The patient had a high pancreatic polypeptide level of 1,830 ng per liter (normal, 150). Administering cisplatin, cyclophosphamide, doxorubicin, and prednisone resulted in substantial palliation. The patient's pancreatic polypeptide level continues to be elevated.

Case 3

The patient, a 64-year-old man, consulted his physician about a dull pain in the left side of his chest. A roentgenogram showed an anterior mediastinal mass that was resected and diagnosed as a thymoma. Nine years later, a chest roentgenogram done routinely before the surgical repair of a fractured wrist showed that the tumor had recurred. A partial resection was followed by postoperative radiotherapy. A review of the patient's previous slides showed the lesion was a carcinoid tumor of the thymus. His evaluation revealed the following normal values: ACTH (< 18 ng per liter), cortisol (0.456 μmol per liter), urinary 5-HIAA (30.5 μmol per day), serum calcium (2.25 mmol per liter), and serum electrolyte levels. Chemotherapy with cyclophosphamide, doxorubicin, cisplatin, and prednisone yielded good palliation.

Case 4

A routine chest x-ray film taken of a 50-year-old man showed an anterior mediastinal mass. Radical excision of the mass revealed a thymic carcinoid tumor that, with immunoperoxidase, stained positive for neuron-specific enolase. Electron microscopy revealed neurosecretory granules, and a laboratory evaluation showed normal serum electrolyte and calcium levels. The patient had no signs of endocrinopathy. Postoperative radiotherapy was advised, but he did not return for follow-up.

Case 5

The patient, a 38-year-old man, had a routine chest x-ray film that showed an anterosuperior mediastinal mass. The mass was resected, diagnosed as a thymoma, and the patient received radiotherapy postoperatively. Five years later, a chest roentgenogram taken because of the patient's right shoulder and chest pain revealed a recurrent mediastinal mass. He underwent a second operation two years later for resection of the mass and the superior vena cava. Metastases to the right lung were noted postoperatively, and the patient received doxorubicin. When a right pleural effusion developed, he was referred to MD Anderson Cancer Center.

A review of the patient's slides showed a carcinoid tumor of the thymus, and cytologic assay of the pleural fluid showed it to contain malignant cells. After the patient underwent pleurodesis, he was treated with combination chemotherapy that included doxorubicin and lomustine. He did well for ten years and then died while undergoing coronary artery bypass grafting. At no time did he show any clinical signs of an endocrine disorder, and his serum calcium level was always within normal limits.

Case 6

The patient, a 44-year-old woman, consulted her physician about pain in the right shoulder and a dry cough. A chest x-ray film showed an anterior mediastinal mass. She underwent a thoracotomy for removal of a large thymic tumor, which was interpreted pathologically as a benign thymoma. The patient's postoperative course was complicated by a mediastinal abscess. Two months later, she underwent radiation therapy. She then came to MD Anderson Cancer Center.

A review of her slides revealed a carcinoid tumor of the thymus, and her history disclosed that her sister had had pituitary and parathyroid tumors removed in the past. According to her laboratory evaluation, the patient had a calcium level of 2.82 mmol per liter (normal, 2.20 to 2.50); phosphate, 0.64 mmol per liter (normal, 0.80 to 1.60); urinary calcium, 10.39 mmol per day (normal, 1.2 to 3.6); C-terminal parathormone, 155 pmol per liter (normal, <6 to 40); serum serotonin, less than 22 pg per ml; urinary 5-HIAA, 20 μmol per day; normal 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels; normal calcitonin; normal vasoactive intestinal polypeptide; pancreatic polypeptide, 1,430 ng per liter (normal, 0 to 150); normal glucagon, 41 ng per liter; normal gastrin; prolactin, 21.2 nmol per liter (normal, 0.08 to 6.0); and 8 AM plasma cortisol, 278 nmol per liter (normal, 222 to 416). A CT scan revealed multiple pulmonary nodules, consistent with metastases. Skull x-ray films were normal. She underwent a subtotal parathyroidectomy, and tissue was implanted in the left forearm.

Table 1 contains a brief summary of the six patients' histories.

Discussion

Carcinoid tumors are derived embryologically from the neural crest and usually develop in the gastrointestinal tract. Since the first report of eight cases of thymic carcinoid tumor,[1] its associations with the Cushing's syndrome and multiple endocrine neoplasia have been characterized. This rare tumor occurs predominantly in men. All 8 patients described by Rosai and Higa,[1] 12 of the 15 patients reported by Wick and co-workers,[3] and 5 of our 6 patients were men.

Patients with these tumors often are asymptomatic, and the tumors are discovered incidentally on a routine chest x-ray film. In the original report,[1] three of the eight patients were asymptomatic, and in four of our six patients, tumors

TABLE 1.—*Features of 6 Patients With Carcinoid Tumor of the Thymus*

Patient No.	Age at Diagnosis, yr	Sex	Clinical Features	Location of Mass	Hormone Production	Carcinoid Syndrome	Associated Endocrinopathies	Metastases	Therapy	Survival
1 . .	18	♂	Cushing's syndrome	Anterior mediastinum	ACTH	No	Cushing's syndrome	Bones	Surgery, XRT, chemo	Living, 5 yr
2 . .	33	♂	Asymptomatic	Anterior mediastinum	None	No	None	Lungs, bones, adrenal glands	Surgery, chemo	Living, 7 yr
3 . .	64	♂	Asymptomatic	Anterior mediastinum	None	No	None	None	Surgery, XRT, chemo	Living, 16 yr
4 . .	50	♂	Asymptomatic	Anterosuperior mediastinum	None	No	None	. . .	Surgery	2 yr at least
5 . .	38	♂	Asymptomatic	Anterosuperior mediastinum	None	No	None	Lungs	Surgery, XRT, chemo	10 yr
6 . .	44	♀	Dry cough	Anterior mediastinum	None	No	Hyperparathyroidism, probable MEN syndrome	Lungs	Surgery, XRT	Living, 1 yr

ACTH=adrenocorticotropic hormone, chemo=chemotherapy, MEN=multiple endocrine neoplasia, XRT=radiotherapy

were discovered on routine roentgenograms. Two of eight patients in the series of Rosai and Higa presented with shoulder pain,[1] as did one of ours; other symptoms we saw were dyspnea and chest pain.

Endocrine manifestations may be seen in a third of patients, Cushing's syndrome caused by elevated ACTH production being the most common. Of 15 patients reported by Wick and associates, 5 had Cushing's syndrome.[3] The secretion of ACTH by the tumor may be partially responsive to plasma cortisol levels.[4] Hyperparathyroidism as part of the multiple endocrine neoplasia syndrome type I can occur as well.[5] In contrast to all the other reported cases occurring in men, our patient with a thymic carcinoid tumor and a probable syndrome of multiple endocrine neoplasia is a woman. The review of 74 cases by Wick and colleagues did not include one woman with this thymic carcinoid association[6]; the three patients described by Rosai and co-workers with this association were all men,[2] as were the six patients reviewed by Salyer and colleagues.[7] Hereditary hyperparathyroidism and one patient with probable inappropriate antidiuretic hormone secretion in association with thymic carcinoid tumor have also been described.[8,9] To date, in contrast to other foregut carcinoids, none of the reported thymic carcinoid tumors have been associated with the carcinoid syndrome.

Thymic carcinoids may be confused with epithelial thymomas, which carry an entirely different prognosis. Three of the six patients in our series had an original diagnosis of thymoma. In contrast to thymomas, however, thymic carcinoids are apudomas. Staining for neuron-specific enolase may help in the diagnosis,[10] as we found in the one patient for whom this was done, and electron microscopy may reveal electron-dense granules.[11] Furthermore, the tumor cell may stain positive for a variety of hormones including ACTH, calcitonin, and cholecystokinin.[11] Thymic carcinoid tumors are usually locally invasive and frequently metastasize, usually to the lungs and bones. As shown in Table 1, four of our six patients currently have metastases. Local recurrence is common and may be associated with recurrence of endocrine manifestations.

Surgical excision probably offers the best chance of a cure. Radiotherapy may control persistent and recurrent tumors,[7,12-14] and chemotherapy with different protocols from those for thymomas may be a useful palliative measure.[15-17] Long survival is not uncommon, even after metastases develop (Table 1). The one of our patients who died did so ten years after diagnosis and from an unrelated cause; no follow-up information is available on another of our patients, who lived for at least two years following the diagnosis. Patients with metabolic abnormalities resulting from the Cushing's syndrome may have a worse prognosis than patients without this associated condition.[7,9]

Carcinoid tumor of the thymus should be considered in the differential diagnosis of anterior mediastinal masses. Endocrinologic manifestations are common and should be looked for, and prolonged survival is not uncommon even when metastases occur.

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Correspondence

The Editors will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words and must be typewritten, double-spaced, and submitted in duplicate (the original typescript and one copy). Authors will be given the opportunity to review the editing of their correspondence before publication.

Confidential Versus Anonymous Human Immunodeficiency Virus Antibody Testing

To THE EDITOR: The question of whether the names of persons tested for the human immunodeficiency virus (HIV) should be obtained continues to be controversial. One reason for the controversy is the concern that there will be breaches of confidentiality, resulting in insurance, employment, housing, and social discrimination. Despite the superb record of public health agencies in protecting confidential records, advocates of anonymous testing argue that fear of loss of confidentiality may cause persons at risk for HIV infection to avoid counseling and testing unless anonymous testing is offered.[1] This argument was ostensibly bolstered by a study conducted in Oregon in which it was shown that the number of gay men who were tested increased by 125% in the first four months after the option of anonymous testing was available.[2] Fehrs and colleagues compared testing data in Oregon with those in Colorado and California.[2] It is important to point out that the increased number of gay men tested in Oregon after the change (108 per month) did not approach the baseline number of gay men tested in Colorado during the same time period (254 per month).

In Colorado, the reporting by name of HIV-antibody-positive persons has been required by regulation or statute since November 1985. All testing is done confidentially. In light of the Oregon study and the letter of Kegeles and coworkers,[1] we compared testing rates and seropositivity rates at the 12 public counseling and testing sites in Colorado with those of the 33 public counseling and testing sites in Oregon during 1987 and 1988. Mid-1987 population estimates were used as denominators, and the Poisson distribution was used to test differences in rates. Oregon data and population statistics were provided by the Oregon State Health Division. We estimate there are 100,000 gay men in Colorado (30.2% of never-married men aged 15 to 59 years); because the male population of Oregon was 80.5% of that in Colorado, we estimated there were 80,500 gay men in Oregon.

TABLE 1.—*Comparison of HIV Tests and Rates at Public Counseling and Testing Sites (1/1/87 through 12/31/88)*

	Colorado		Oregon	
	No. of Tests	Rate*	No. of Tests	Rate*
Total	24,377	739.5†	16,184	601.6
Male	14,199	866.0†	9,084	688.6
Female	10,178	614.4†	6,974	508.7
Gay men	5,100	5,100.0†	3,792	4,710.6
History of IV drug use	3,133	95.1‡	2,511	93.4‡
	Colorado		**Oregon**	
	No. Positive	Rate*	No. Positive	Rate*
Total	1,029	31.2	797	29.6
Male	967	59.0	764	57.9
Female	62	3.7‡	30	2.2
Gay men	835	835.0	702	872.0
History of IV drug use	186	5.6†‡	38	1.4‡

IV=intravenous

*Per 100,000 population.
†Statistically significant difference in rates, $P<.05$.
‡Total state population used as denominator.

The rate of gay men tested in Colorado was significantly higher than in Oregon (Table 1), as were Colorado testing rates for the total, female, and male categories. Colorado seropositivity rates were significantly higher in two categories—women and intravenous drug users—and not significantly different for the total, male, and gay male categories.

It is important not to overinterpret testing data. Comparisons between programs should include population-based rates and account for access to counseling and testing sites, availability of testing and counseling in other facilities such as sexually transmitted disease clinics, and the effect of advertising of testing services. Evaluation of a counseling and testing program should not be based solely on the number of persons tested or the number of persons testing seropositive. The number of persons who return to obtain their results and receive post-test counseling and the number of sex and needle-sharing partners referred for counseling and testing are also important considerations. In addition, seropositivity rates are dependent on regional differences in the prevalence of HIV infection.

The comparison of testing in the two states does not support the contention that substantially fewer gay men are tested when only confidential testing is available. On balance, we are pleased with the gay community's response to the Colorado testing program and with the major contribution the reporting requirement has made to our ability to provide services to HIV-positive persons, including gay men.

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The Cost of Medicine

To THE EDITOR: One practical answer to the cost of medicine is prescription drug insurance. But something must be done about those policies that pressure the physicians to write for far more medication at a time than they think is appropriate for a given patient. What do you say to patients who explain that their pills cost almost $3 but that if you write for a three months' or a six months' or sometimes even a year's supply,

n a prescription insurance requirement, the entire script will still cost them only that same $3?

The false economies of forced minimal script writing appall me. We all know that patients will have allergic or other unpredictable reactions to almost any medication. My usual (when unfettered) custom is to write for a one- or two-week supply, then have the patient phone me and, if appropriate, refill the prescription for the long term, satisfied that the patient is at least tolerating the medicine. But lately I hear, "Doc, my insurance covers all my prescriptions, but you have to give me enough for three months (or six months)." The implication is that it is to the patients' economic advantage to throw 100 or 200 pills down the toilet if they do not like them or if they perceive that they somehow do not help. Yet with the cost of prescriptions as high as it is, what is the physician to do? Economic self interest is certainly on the patient's side.

Insurance for prescriptions is a boon to us all. Some patients with chronic diseases save hundreds, even thousands, of dollars a year. Without such insurance many of them would have to forego medicines that we must prescribe and that they badly need. I realize that buying and selling in quantity saves money, but I cannot believe the economics that dictate that writing for a minimal three-month supply of medicine instead of a preliminary trial of one week or one month can account for the difference between a $3 prescription and a $100 prescription or that a patient must have my written prescription for a year's supply of medicine or be financially penalized. After all, these are powerful drugs we are authorizing, not stocking the freezer with a side of beef!

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National Health Insurance in America—The Issue of Copayment

To THE EDITOR: Dr Grumbach's well-written article in the August 1989 issue about the need for national health insurance[1] *almost* converted me to become a believer in it. The reason for the almost is that I have been in ardent opposition to national health insurance for the past 30 years because of the firsthand experience I gained in my own country, Hungary. In Hungary, national health insurance is bad for the patients and bad for the physicians. Of course, Dr Grumbach didn't propose to copy the Hungarian way of national health insurance; he suggests copying that of the Canadian system. In the same issue, the editorial, "A View From Canada," by Dr Banks indicated that the Canadian system also has many shortcomings and is not a solution either.[2]

I see the point, however. Now, as my grown-up children are joining the labor force, they are at the same time joining the 37 million uninsured in the job marketplace. I am concerned, not so much about the possible decline of my future income but about the health care of my children without insurance.

Now that communism has failed in every aspect of life, how can anyone recommend any form of national health insurance? A solution has to be found, though.

So, how can the national health insurance system work in the framework of free enterprise, be fair to everyone, and become even better than the Canadian experience? The key, I believe, is that patients shouldn't be relieved of total responsibility for their own health care, as Dr Banks pointed out. Human nature should be taken into account in order to prevent bankruptcy of the system. In order to avoid bankruptcy, the system should be set up in such a way as to avoid abuse. It appears to me that this can be done best with copayments.

I suggest making copayments on a sliding scale and excluding catastrophic illnesses so as to not hurt the poor.

I believe in these copayments because of what I have experienced in my own practice. All Medi-Cal patients are supposed to pay $1 per visit. Most physicians do not enforce this policy for one reason or another. I didn't either, but recently I started asking for $1 copayment, and I was amazed to see how the number of cases of recurring vaginitis and cystitis, vague abdominal and back pains, and so forth decreased. Based on this experience, I have started to believe in the concept of copayments, which help to decrease abuse of the system. With copayments, national health insurance may work.

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Alopecia Universalis in Autoimmune Polyglandular Syndrome Type I

To THE EDITOR: We read with special interest the report of Imam and co-workers in the September 1988 issue on the occurrence of alopecia universalis in a patient with autoimmune polyglandular syndrome type I.[1] During the past 16 years we have been following a very similar patient, a boy who presented at the age of 3 years with alopecia areata of the scalp. Signs of mucocutaneous candidiasis involving the oral mucosa and the fingernails developed the following year. Later, hypoparathyroidism (at age 5 years), uveitis (at age 7), and Addison's disease (at age 8) were diagnosed. The alopecia progressed from areata into universalis within four years, with loss of all body hair, including eyebrows and eyelashes. Pubertal development—such as testicular growth—was first observed at age 11. Plasma testosterone levels increased gradually to adult values, and basal plasma gonadotropin levels were normal. The patient's voice modulated normally, and he reported conscious ejaculations at age 14 years. Adult testicular volume was reached at 16 years, but no sexual hair appeared at any stage of puberty.

Because of cataract, both lenses were removed when the patient was 12. Primary hypothyroidism and vitiligo developed at age 18 years. An elevated titer of antiadrenal antibodies—but not of any other autoantibodies—was found, indicating a possible autoimmune pathogenesis of the disease. Like Imam and colleagues' patient, this patient had severe emotional problems related partly to his physical appearance and alopecia, and noncompliance with his medication regimen resulted in frequent episodes of hypocalcemia and, on one occasion, serious hypercalcemia due to vitamin D intoxication.

We think that our data on this patient support the assumption of Imam and associates that alopecia universalis might be a feature of autoimmune polyglandular syndrome type I and not just a coincidental association. Of particular interest

is that in our patient alopecia was the presenting sign of the syndrome preceding the endocrine abnormalities.

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Electroconvulsive Therapy Use During Pregnancy

To THE EDITOR: In the September 1989 issue, Guze and Guze very aptly discussed the concerns about the use of psychotropic medication during pregnancy,[1] and Kerns editorially expanded on the discussion of this dilemma, stressing the need to manage a patient with nonbiologic treatments.[2] This often is not successful in patients with severe psychiatric disorders, and some type of somatic therapy is needed to resolve a severe depression, catatonic state, or other psychotic condition. Elsewhere in the same issue, Gerner stated that electroconvulsive therapy (ECT) should be "included as an early intervention" in the treatment of intractable depression.[3] No discussion of ECT is present in either of the above discussions of psychiatric treatment during pregnancy.

Electroconvulsive therapy given during pregnancy has been shown to be both effective and safe for mother and fetus in many published case reports. Sobel concluded that ECT does not increase fetal mortality and morbidity; on follow-up, children born to mothers who had ECT developed normally.[4] Repke and Berger indicated that ECT may be the treatment of choice for the acutely depressed pregnant patient.[5]

A review by Gelenberg suggested that ECT may be helpful in the treatment of some cases of depression, mania, or psychosis during pregnancy.[6] Summarizing the current state of the literature, Abrams concluded, "ECT is not known to exert any such adverse fetal effects . . . and should be used in preference to drugs in pregnant women and during the nursing period."[7(p26)] He argued that excessive monitoring is not necessary.

Severe psychiatric illness affects not only the mother but the fetus, as well. Maternal disregard for health issues, poor food and liquid consumption, an altered biochemical environment of the mother, such as abnormal cortisol circadian rhythm, and attempted suicide could all adversely affect the developing fetus. Electroconvulsive therapy should be at least considered as a possible option for all patients during pregnancy and recommended when appropriate.

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Dialysis Disequilibrium Syndrome

To THE EDITOR: The article by Drs Harris and Townsend on the dialysis disequilibrium syndrome in the July 1989 issue[1] omits important information. If rapid dialysis in an acutely uremic patient is the major cause of this syndrome, the reader should know the size of the artificial kidney used, the blood flow, and the weight of the patient. The early literature on the subject always described it as probably due to the osmotic effect of rapid decline in blood urea and other osmotically active substances. The report by Drs Harris and Townsend[1] points out several clinical studies that do not support this explanation. Arieff and associates[2] described using mannitol and glycerol in the dialysis solutions in studying experimental cerebral edema in dogs. They were able to prevent brain edema in dogs with the use of glycerol and suggested that its addition to dialysate might be effective in preventing the dialysis disequilibrium syndrome.

For many years I have used a smaller kidney and/or a lower blood flow of 100 ml per minute for the first hour and then 150 ml per minute during the first dialysis; I have usually limited this dialysis to about two hours. I have not encountered dialysis disequilibrium for about the past 22 years by using these precautions.

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Drs Harris and Townsend Respond

To THE EDITOR: We wish to thank Dr Levin for his comments about the dialysis disequilibrium syndrome. Our patients undergoing dialysis for the first time are also put on a smaller kidney, and the blood flow is at a slower rate than that used for chronic dialysis patients. Although occasional patients have transient headaches, the patient discussed in our report was the only one to suffer such dire effects since the dialysis unit opened more than ten years ago. The flow rate used for those undergoing their first dialysis ranges from 200 to 250 ml per minute, in contrast to rapid dialysis done at 450 to 500 ml per minute. The patient described was dialyzed at a rate of 250 ml per minute on a CA90 dialyzer, which has a surface of 0.9 m^2 and is smaller than those used for chronic dialysis.

There is still controversy concerning all of the causes of the dialysis disequilibrium syndrome. We pointed out the various papers on the subject including the paper cited by Dr Levin written by Arieff and associates. Fortunately, this is a rare syndrome today. We presented the case simply to remind others that it can occur even under standard conditions of dialysis.

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Public Health and Preventive Medicine

Vitamin A—A Pregnancy Hazard Alert

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This is one of a series of articles from western state public health departments.

Vitamin A is essential to human health, but concerns have arisen recently regarding its potential teratogenicity. Human and animal birth defects have been associated with the use of the vitamin A analogue, isotretinoin, or Accutane, for acne treatment, although the association of such defects with vitamin A itself is unclear. The federal Food and Drug Administration is evaluating the health issues surrounding vitamin A and, together with the manufacturer, has developed restrictions and label warnings to ensure the appropriate use of Accutane. We also have evaluated these issues, with concerns about the possible teratogenicity of high vitamin A intake during pregnancy. Practitioners should be familiar with the possible hazard of excessive dosages of vitamin A and its analogues. Vitamin A daily doses of higher than 8,000 IU for pregnant woman are not necessary for good health and are not recommended. Foods high in β-carotene can provide the necessary amounts of vitamin A and, in contrast to the synthetic analogues, their use has not been associated with vitamin A toxicity or teratogenicity in humans or animals.

(Kizer KW, Fan AM, Bankowska J, et al: Vitamin A—A pregnancy hazard alert. West J Med 1990 Jan; 152:78-81)

The essentiality of vitamin A for normal human health is well known. Likewise, problems of vitamin A deficiency and hypervitaminosis A have been recognized for many years. Concerns about the potential teratogenicity of vitamin A and its synthetic analogues have arisen only recently. Practitioners need to be aware of these concerns.

Vitamin A is essential for normal cellular function and growth, the proliferation and differentiation of epithelial tissues, and to maintain visual and reproductive functions.[1] In the United States, vitamin A deficiency is rare and is usually associated with severe chronic malnutrition, especially in children. Vitamin A deficiency can result in skin lesions such as follicular hyperkeratosis; keratomalacia and visual impairment; keratinization of the bronchorespiratory tract; pathologic changes of the epithelium of the urinary tract (which can lead to urinary calculi), gastrointestinal tract, and sweat glands; faulty modeling of bone; and abnormal reproductive functions, including impaired spermatogenesis, testicular degeneration, spontaneous abortion, fetal resorption, and fetal malformations. The most notable impairment resulting from vitamin A deficiency is classic night blindness.

Vitamin A deficiency is treated with vitamin A dietary supplementation as retinol or retinyl ester preparations. Similarly, various synthetic vitamin A supplements are available for use to prevent vitamin A deficiency during periods of increased physiologic demand such as during pregnancy, lactation, and infancy. Other retinoids, such as tretinoin and isotretinoin (13-*cis*-retinoic acid), are used to treat skin disorders such as cystic acne, pustular psoriasis, keratosis follicularis (Darier's disease), and ichthyosis.[1] The clinical use of these compounds, however, is often limited by side effects observed at therapeutic dosages.

Although the effects of hypervitaminosis A on the integumentary, skeletal, reticuloendothelial, and central nervous systems have long been recognized, the potential for adverse developmental effects of vitamin A is less well known. Concern about excess intake of vitamin A during pregnancy has increased in recent years because of its structural and metabolic relationships to other retinoids, especially 13-*cis*-retinoic acid (isotretinoin, or Accutane), a synthetic retinoid that has a teratogenic potency in humans similar to thalidomide and rubella (C. Grabowski, MD: Statement on behalf of the Teratology Society to the US Food and Drug Administration [FDA] concerning isotretinoin, April 26, 1988).

Isotretinoin (Accutane or Roaccutane) has been used since 1982, when it was first marketed as an oral agent for treating recalcitrant cystic acne.[2] More recently, an evaluation of 154 pregnancies with exposure to the drug showed that 14% (21 cases) resulted in malformed infants, 17% (26 cases) in infants without major defects, 8% (12 cases) in spontaneous abortions, and 62% (95 cases) in elective abortions.[3] The risk for serious birth defects in infants of pregnant women with exposure to isotretinoin was determined to be about 25%. Another report showed that isotretinoin administered orally to 64 women during the first trimester of pregnancy resulted in 34 cases of fetal defects and 30 cases of spontaneous abortion.[4] Defects have involved pathologic changes in the central nervous system, facial malformations

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ABBREVIATIONS USED IN TEXT

CDHS = California Department of Health Services
FDA = Food and Drug Administration

with small or absent external ears, and cardiovascular impairments. The total number of infants with birth defects consistent with those associated with isotretinoin use is unclear, with the estimates ranging from 62 to 1,300 (P. M. Bossey, "Maker of Drug for Acne Calls Birth-Defect Report 'Invalid,'" *New York Times,* April 23, 1988, p 1).

Human birth defects and spontaneous abortions have been associated with the use of etretinate (Tegison, United States; Tigason, Europe), the trimethylmethoxyphenyl ethyl ester analogue of all-*trans*-retinoic acid (analogue of vitamin A acid) (Roche Laboratories, Division of Hoffmann-LaRoche, Inc: Statement made to the FDA Advisory Committee and public hearing on etretinate safety).[1] Etretinate is currently approved for use in the treatment of psoriasis.[1] In Europe, seven cases of fetal malformations due to etretinate exposure during pregnancy were reported; these included meningomyeloceles, craniofacial and skeletal abnormalities, severe brain defects with anophthalmia, and low-set ears.[1] A case of congenital malformation was reported in a child born to a woman from Brazil who had discontinued etretinate therapy almost a year before she conceived.[5] There have been no reports of birth defects associated with its use in the United States, but it was approved only in late 1986 (*FDA Consumer,* October 1988, pp 27-29). The lowest human teratogenic doses for the two retinoids, isotretinoin and etretinate, are estimated to be 0.4 and 0.2 mg per kg per day, respectively.[6] Etretinate is, therefore, more potent than isotretinoin, and its teratogenic effect may persist longer than isotretinoin's.

Vitamin A is metabolized to the all-*trans*-retinoic acid, which differs from isotretinoin (13-*cis*-retinoic acid) only in the direction of the acid tail. All-*trans*-retinoic acid also produces 13-*cis*-retinoic acid as a metabolite. Whether vitamin A itself (as retinol or retinyl esters) is a human teratogen is unclear. There have been several isolated case reports of human birth defects with high levels of maternal vitamin A exposure.[7] Some of the malformations are consistent with the pattern of defects produced by isotretinoin, but a causal relationship has not been established. Although poor exposure surveillance confounded by the simultaneous intake of other nutritional supplements makes the available data inconclusive, the evidence certainly raises concerns about possible human teratogenicity of high doses of vitamin A.

Isotretinoin, etretinate, and vitamin A as retinol or retinyl esters have been confirmed as embryotoxic and teratogenic in studies of animals.[8] These findings contrast with those related to naturally occurring carotenoids, which are biotransformed in mammals to vitamin A and have not been identified as teratogenic or embryotoxic in studies of either animals or humans.

The many biologic effects of vitamin A and its derivatives are summarized in Table 1.

The existing guidelines from the manufacturer (Hoffmann-LaRoche Inc) for the use of Accutane by women are specific and detailed.[9] They stress the necessity of obtaining a negative pregnancy test two weeks before initiating therapy with Accutane and the importance of using an effective form of contraception a month before, during, and for a month after taking Accutane. Women who become pregnant while using isotretinoin are advised to discuss with their physicians the advisability of continuing the pregnancy. Despite these restrictions and warnings to physicians and consumers, women taking Accutane continue to become pregnant and produce malformed infants (*FDA Consumer,* October 1988, pp 27-29 and Centers for Disease Control, unpublished data, cited by C. Grabowski). More vigilant supervision in the use of the medication seems necessary.

To consider the isotretinoin issues, the FDA convened a meeting of its Dermatologic Drugs Advisory Committee in April 1988, with representatives from the Centers for Disease Control, the American Academy of Pediatrics, the American Academy of Dermatology, and consumer advocates (*FDA Consumer,* October 1988, pp 27-29). After considering advice from consumer and professional organizations, the FDA and Hoffmann-LaRoche developed further restrictions and unprecedented labeling warnings to ensure the appropriate use of the drug, with the hope of eliminating the associated birth defects. At this time, the FDA plan calls for the following:

- Physician labeling providing
  A stronger, boxed warning statement with large print.
  Affirmation in the statement that the drug is *not* to be used for a woman of childbearing age unless her physician determines that she meets all six of the following criteria:
  1. She has severe disfiguring acne.
  2. She can understand and carry out instructions.
  3. She is capable of complying with mandatory contraceptive measures.
  4. She has received oral and written warnings of the hazards of pregnancy while taking Accutane.
  5. A pregnancy test within two weeks of initiating therapy was negative.
  6. The drug's use will not begin until the start of the next normal menstrual period.

  A prominent non-pregnancy symbol—outline of a pregnant woman inside the international crossed circle meaning "not" or "don't"—is added at the beginning of the label and in drug labeling printed in the *Physicians' Desk Reference.*[10]
  There is clear labeling that the drug should be prescribed only by physicians who have special competence in the diagnosis and treatment of severe cystic acne.
- Patient labeling details the following:
  An extremely high risk—one chance in four, or greater—that a deformed infant will result if a women becomes pregnant while taking Accutane.
  A photograph of an infant with characteristic visible external deformities incurred from exposure to Accutane.
  The non-pregnancy symbol on *each* page of the patient material and on *each* panel of the "blister pack." (Accutane must only be dispensed in a blister pack containing patient warnings and other information in the package, in addition to the currently used pamphlets physicians and pharmacists are asked to give patients.)
  A consent form, with a discussion of fetal abnormalities.
  A statement that each new prescription or refill should be started only on the second or third day after the start of a normal menstrual period.

TABLE 1.—*Beneficial and Adverse Health Effects of Vitamin A and Derivatives*

Vitamin A and Derivatives	*Chemical Name*	*Class*	*Source*	*Biologic/Therapeutic Function*	*Deficiency*	*Toxicity*	*Source*
Retinol, or vitamin A	...	Retinoid	Natural: fish oil, liver, cheese, butter, egg yolk Synthetic: retinol or retinyl esters	Maintains growth and visual and reproductive functions; regulates proliferation and differentiation of epithelial tissues	Functional impairments and structural changes in organs and systems (eye, respiratory tract, skin, genitourinary system, gastrointestinal tract, sweat glands, bone); night blindness; disturbances in epithelial differentiation of mucus-secreting or keratinizing tissues	Natural sources of vitamin A have not been associated with toxicity except for that from consuming certain mammalian livers; toxicity has resulted from synthetic vitamin A preparations as retinol and retinyl esters Acute poisoning: severe headache, drowsiness, irritability, vomiting, hepatomegaly, dizziness, papilledema, skin peeling, increased intracranial pressure Chronic poisoning: effects on skin, central nervous system (headache, fatigue, irritability), bones, and liver; teratogenic in animals; birth defects in humans suggested but unconfirmed	Mandel and Cohn, 1985[1]; Lammer, 1988[5]; FDA*
Provitamin A (vitamin A precursor)	...	Carotenoids (β-carotene)	Natural sources include carrots, tomatoes, green beans, and other red, yellow, and green vegetables	Biotransformed in mammals to vitamin A	...	Considered nontoxic; has not been associated with vitamin A toxicity	Mandel and Cohn, 1985[1]
Retinal (vitamin A aldehyde)	Retinaldehyde	Retinoid	Metabolic product of vitamin A, aldehyde form	Essential for adaptation to the dark	...	...	...
Retinoic acid, *trans* (vitamin A acid)	Tretinoin (Retin A)	Retinoid	Metabolic product of vitamin A, acid form	A topical cream and lotion used to treat acne (and recently associated with easing wrinkles) FDA pregnancy category B: should be used in pregnancy only when clearly needed Not extensively absorbed	...	Animal teratogen	Roche Labs†; Lammer, 1988[5]; FDA*
Retinoic acid, 13-*cis*	Isotretinoin	Retinoid	Synthetic; also a metabolite of all-*trans*-retinoic acid	Oral therapeutic agent (Accutane or Roaccutane) for treating acne and other acneform diseases FDA pregnancy category X: should not be used in pregnant women or in those likely to become pregnant	...	Human and animal teratogen	Mandel and Cohn, 1985[1]; Teratology Society‡; Lammer et al, 1985[3]; Willhite et al, 1986[4]; Roche Labs†; Lammer, 1988[5]; FDA*
Retinoic acid, all-*trans*, trimethylmethoxyphenyl ethyl ester	Etretinate	Retinoid (aromatic)	Synthetic	Oral therapeutic agent (Tegison) for treatment of psoriasis FDA pregnancy category X: should not be used in pregnant women or in those likely to become pregnant	...	Human and animal teratogen	Mandel and Cohn, 1985[1]; Roche Labs†; Lammer, 1988[5]; FDA*

FDA=US Food and Drug Administration

FDA Consumer, October 1988.
†Roche Laboratories, Division of Hoffmann-LaRoche, Inc, in a presentation to FDA Advisory Committee and a public hearing on etretinate safety, June 1985.
‡C. Grabowski made a statement on behalf of the Teratology Society concerning isotretinoin to the FDA, April 26, 1988.

A phone number for additional information on possible pregnancy.

- External educational campaigns are carried out aimed at physicians, pharmacists, and patients, along with advertisements published on the teratogenic effects of the drug.
- The firm's plan to provide gynecologic consultation and contraceptive counseling to patients is reviewed.
- A tear-off, prepaid postcard is included, addressed to the manufacturer and requesting the patient's name, telephone number, address, and permission to be contacted by the company for required studies.
- The company does a follow-up survey to ascertain patient awareness, disease status, contraceptive use, any pregnancy that occurs, and the outcome.
- The manufacturer reports all pregnancy exposures—occurrence of any adverse reaction or birth defects.
- The manufacturer increases its attempts to find out why some patients, despite warnings, get pregnant or use the drug when already pregnant—that is, did pregnancy occur through testing or contraceptive failure, ignorance, or willful disregard of the warnings?
- The usage data for Accutane are analyzed quarterly, stratified by age and sex.
- A new study of Accutane is developed by the manufacturer using lower doses or higher doses for a shorter period of time.

Because vitamin A dietary supplements are considered a food, not a drug, health hazard warnings are not required on them. In addition, the teratogenicity of vitamin A for humans has not been definitively established, so labeling informing about possible hazards for fetuses is not obligatory. Various synthetic preparations containing 25,000 international units or more of vitamin A (as retinol or retinyl esters) per unit dose are readily available for over-the-counter sale, and their use continues to be encouraged by some persons. According to an FDA telephone survey, 4.3% of vitamin A users in the United States were taking five times more than the Food and Nutrition Board's recommended dietary allowance (C. Grabowski: Statement on behalf of the Teratology Society to the FDA concerning isotretinoin, April 26, 1988). In addressing this issue, the American Teratology Society recommended the following actions[7]:

- Women in their reproductive years should be informed that the excessive use of vitamin A shortly before and during pregnancy could be harmful to their babies. (A bioaccumulation of vitamin A from continuously high doses is also a concern.)
- Manufacturers of vitamin A (as retinol or retinyl esters) should lower the maximum amount of vitamin A per unit dosage to 5,000 and 8,000 IU (1,500 and 2,400 retinol equivalents) and identify the source of the vitamin A.
- The labeling of products containing vitamin A supplements (as retinol or retinyl esters) should indicate that consuming excessive amounts of vitamin A may be hazardous to the embryo or fetus when taken during pregnancy and that women of childbearing potential should consult with their physicians before consuming these products.

The California Department of Health Services (CDHS) is concerned about the possible teratogenic effects of high vitamin A intake during pregnancy and has encouraged federal action requiring health hazard labeling. The FDA is evaluating the health issues surrounding vitamin A, especially considering it as a food for special dietary use. The information will be presented in a monograph in support of affirming its present status of "generally recognized as safe."

In regard to vitamin A intake, the National Research Council's recommended dietary allowance for vitamin A during pregnancy is 5,000 IU obtained from a typical North American diet, with half of the total vitamin A activity provided as retinol and half as carotenoids.[11] An average balanced diet contains approximately 7,000 to 8,000 IU of vitamin A.[7] The US recommended daily allowance established by the FDA is 8,000 IU for pregnant women.[7] Preliminary results from a case-control study on human prenatal exposure to vitamin A suggested that doses lower than 10,000 IU are not teratogenic.[12] Therefore, at this time, higher dosages of vitamin A are not recommended as such dosages are not necessary and may increase the teratogenic risk.

The CDHS considers identifying the source of vitamin A used in the supplements to be important because the natural carotenoids found in common green and yellow vegetables and fruits (β-carotene) have not been associated with vitamin A toxicity or teratogenicity in humans or animals, in contrast to the synthetic vitamin A analogues. Therefore, by relying on foods containing β-carotene as the primary source of these vitamins, women in their reproductive years should be able to easily meet their nutritional needs without incurring the risk of vitamin A toxicity.

The CDHS also recommends that women in their reproductive years, in general, be educated about the possible hazards of megadose vitamin A intake. Practitioners should fully discuss the risks of vitamin A before beginning use in any potentially fertile woman, focusing especially on preventing excessive consumption. The CDHS further recommends that women of childbearing age consult their personal physician before taking *any* medication or vitamin supplement, especially vitamin A, and that this recommendation and a notation of the potential for developmental hazards from excessive vitamin A consumption should be included on the labeling of vitamin A supplements.

The possible teratogenic effect of megadoses of vitamin A is just one example of the ill effects of megavitamin use. The common misconception among the public and among some health practitioners that megadose vitamin intake is only beneficial and carries no health risks underscores the need to educate the public and to provide prescribing information for physicians in this regard.

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Information

Sleep Deprivation and Cognitive Testing in Internal Medicine House Staff

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There is increased concern about the effects of sleep deprivation on physician performance. We administered four standard tests of cognitive function to 23 university hospital house staff. Each physician served as his or her own control, and the tests were administered at rest, after a night on call, and after a night of sleep for recovery. The study was designed so that normal learning would minimize any deterioration in the post-on-call test performance. Statistically significant deterioration occurred in 3 of the 4 tests after a night on call. Even physicians acclimated to sleep deprivation on a regular, every-third-or-fourth-night basis showed functional impairment. The results have implications for patient care under conditions where house staff are stressed by sleep deprivation and prolonged fatigue.

(Robbins J, Gottlieb F: Sleep deprivation and cognitive testing in internal medicine house staff. West J Med 1990 Jan; 152:82-86)

Physicians in residency training programs are required to work for prolonged periods under conditions of sleep deprivation. It is at times of most severe sleep deprivation, that is, "on-call" nights, that residents are most likely to be responsible for the care of acutely ill patients. The therapeutic interventions required at such periods necessitate a high level of psychomotor performance, cognitive function, and emotional equilibrium. The greatest demand on a physician's skills often comes when performance is most likely impaired by sleep loss.

Despite the large amount of research in the field of sleep deprivation, the data regarding physician performance under sleep-deprived conditions are sparse. Existent information implies potentially adverse effects on mood and behavior.[1-8] Although there are notable exceptions,[4,6,9,10] few studies specifically assess the psychomotor and cognitive performance of house staff under conditions of acute sleep deprivation. The classic medical study was published almost 20 years ago when Friedman and co-workers showed that sleep-deprived house staff made more errors when interpreting electrocardiograms.[9] That study addressed one important cognitive aspect of medical practice. There may be more global deterioration of post-on-call house-staff performance.

Deaconson and associates were unable to show the effect of sleep deprivation on surgical residents' performance on psychometric tests.[10] That study used residents on an every-other-night call schedule as their own controls. As pointed out in numerous letters to the editor that followed the original publication, residents in the "control state" may also have been considerably impaired from chronic sleep deprivation.[11]

To better understand the effects of acute sleep deprivation on house-staff performance, we compared the performance of house staff on standardized cognitive tests when rested, after being on call—that is, acute sleep deprivation—and a third time after conditions of normal sleep. The standard on-call schedule at the institution is every fourth night. The control, or rested, evaluations all took place when the resident had been able to get a full night's sleep at home before taking the test. The study was designed in such a way that if previous sleep deprivation had an effect on the results, it would mitigate against the finding of a statistically significant outcome. The session format allowed us to measure baseline functioning and functioning after sleep deprivation and to recheck the baseline, taking into account the normal learning curve.

Methods

Standard tests routinely used in cognitive assessment and rehabilitation were selected to evaluate various cognitive functions. They were administered on a microcomputer terminal with the investigator present at every testing period. The four tests were as follows*:

- *Driver,* in which the subject must maneuver a "car" on a moving track of set width and speed, using a joystick.[12] Scoring is based on percentage accuracy and increased by keeping the car at the bottom of the screen—that is, with less lead time before road hazards appear, which minimizes reaction time. The final score is, therefore, expressed as percentage accuracy and total score. Attention span, eye-hand coordination, and reaction time are assessed.
- *Rapid Number Comparison,* in which four numbers of five digits each are flashed on the screen for approximately 0.5 seconds.[13] Two numbers are identical, and that number

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must be accurately recognized and logged into the computer. Visual reaction time and accuracy, rapid numeric discrimination, short-term memory, and attention span are assessed.

• *Concentration,* in which the subject is presented with a field of characters arranged in a random pattern.[14] A character is selected sequentially by the computer as the target. After the target is located, the subject maneuvers a cursor to cover the character. Scoring is based on the speed of locating the selected character and moving the cursor minus incorrect responses. If a target is not located in a specified time, the subject must start over. Spatial perception, performance under prolonged repetitive conditions, the ability to discern relevant from random information, eye-hand coordination, and the ability to perform under time limitations are assessed. Assistance was given to complete the test to residents who were unable to do this test in the allotted time under post-on-call conditions. Final scoring was affected only in that it allowed test completion for data interpretation.

• *Smart Shopper Marathon,* referred to hereafter as *Math Problems,* is a test in which a subject is presented five sets of simple, high-school level mathematic problems under time limitations.[15] Scoring is based on the number of correct answers in each problem set. There is a time penalty for incorrect answers. Each set requires a minute to complete, and simple mathematic abilities under time limitations are assessed.

The testing period required for these four tests is about 30 to 40 minutes. Each subject who agreed to participate was given a baseline test under conditions of a normal night of sleep for that person. A second test was given under conditions of sleep deprivation. At this second testing period, the volunteering house officer would page the investigator at his or her own convenience before leaving the hospital on completing call night duties (approximately 35 hours from the end of their last normal sleep period). A third and final testing period was given at the convenience of each subject, again under non-sleep-deprived conditions, to determine if change and performance trends under conditions of sleep deprivation would persist after the subjects were rested. Therefore, a change noted in overall performance under conditions of sleep deprivation should revert to baseline if sleep deprivation is the only variable.

TABLE 1.—*Cognitive Testing of Sleep Deprivation—Correlation of Scores (r) in Repetitive Testing (Reproducibility)*

	Before On-Call Night	*After On-Call Night*	*After Recovery*
% Accuracy	0.9277	0.9298	0.8860
Total score, *r*	0.8641	0.9091	0.9495

To assess the reproducibility of results and the validity of these tests, the test with the greatest potential range of scores, *Driver,* was administered a second time at each testing session to 17 of the 23 subjects who agreed to donate the additional time required.

Before doing the test under conditions of sleep deprivation, each subject estimated the amount of sleep obtained on call and the total number of hours since getting a full night's sleep. This is obviously subjective but was intended to make sure none of the subjects had spent two successive nights in a sleep-deprived state, but that all had some degree of sleep deprivation. Baseline assessments were carried out at various times during the normal working day.

In analyzing data, each subject served as his or her own control. No incentive was offered for participation or performance in the study.

Subjects

Members of the house staff in the internal medicine department at the University of California, Davis, Medical Center (Sacramento, California) were asked to volunteer in a study to determine the effects, if any, that sleep deprivation typical of a night on call might have on cognitive performance. In all, 31 of the house staff completed the first battery of tests under conditions of normal sleep. Eight house staff completed the baseline study but were unable to complete the remainder of the study. Of this group, five reported being too tired after being on call and three were not on rotations requiring being on call during the ten-week period of this study. Thus, 23 house staff completed the study. The male-to-female ratio was 16:7, and the distribution of year in training—9 in their first year after graduating medical school, 7 in their second year, 6 in their third year, and 1 in

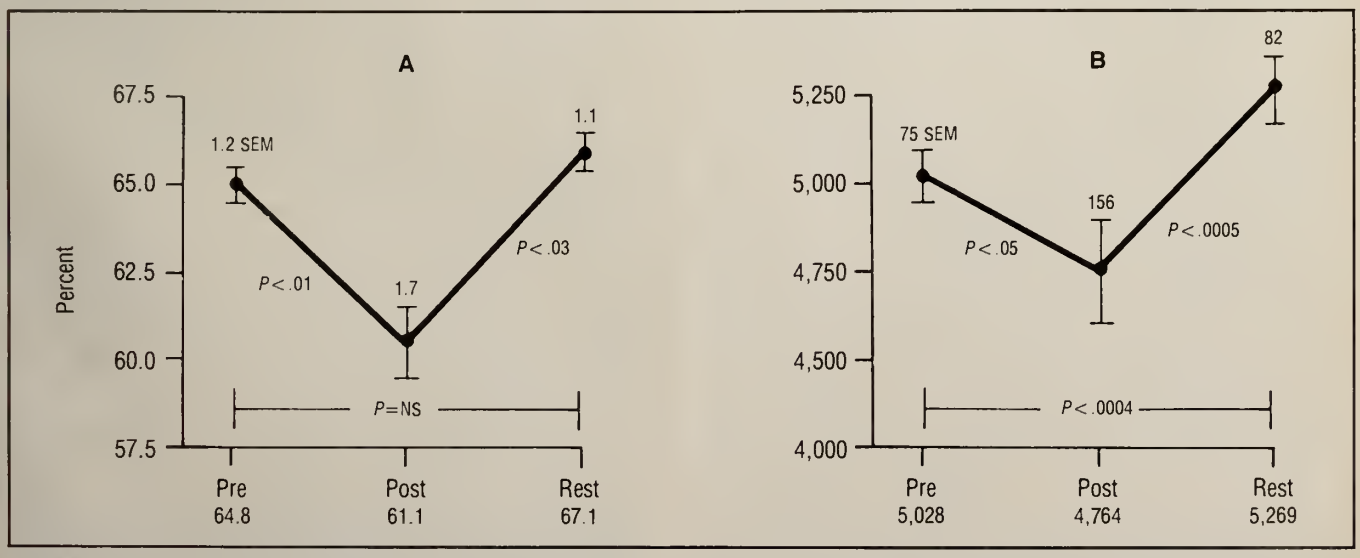

Figure 1.—The graphs show performance results on *Driver* tests before (Pre) and after (Post) being on call and when rested (Rest), with **A** showing the percent accuracy and **B** the total scores indicating speed of response. NS = not significant, SEM = standard error of the mean

the fourth year—represented a valid cross section of the house staff in the Department of Medicine at this university teaching hospital.

Results

Tests were administered under sleep-deprived conditions, averaging 2.1 hours of sleep ± 1.0 hours standard error of the mean (SEM). The total hours awake since the start of on call were 33 hours ± 2.6 SEM. All tests assessing performance under conditions of sleep deprivation were given in the afternoon following on call from 1 to 7 PM.

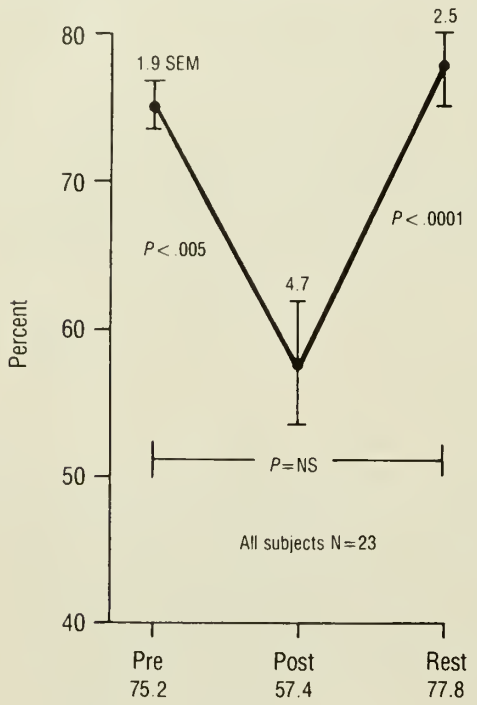

Figure 2.—The graph shows performance results (%) on the *Rapid Number Comparison* test when given before (Pre) and after (Post) being on call and when rested (Rest). NS = not significant, SEM = standard error of the mean

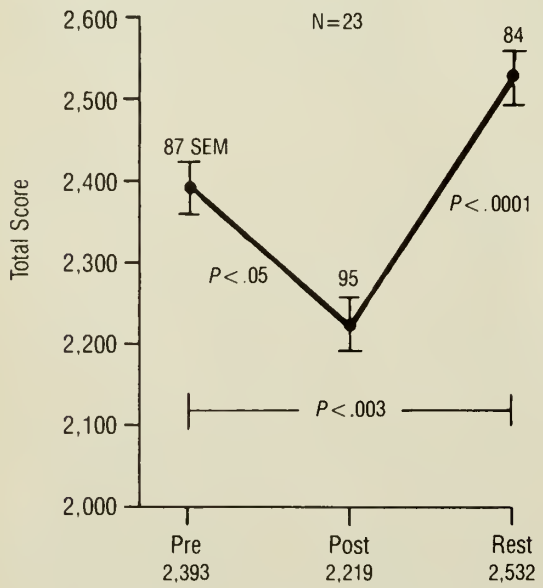

Figure 3.—The graph shows performance results on the *Concentration* test when given before (Pre) and after (Post) being on call and when rested (Rest). SEM = standard error of the mean

Reproducibility

Pearson's correlational analysis was performed on the scores of the 17 subjects who completed the *Driver* test twice in each testing period. As can be seen in Table 1, there is a high correlation between repetitive performances on the same test administered immediately after an initial attempt, with r values ranging from .86 to .95.

Results of Each Test

Paired t tests were used to analyze the results.

The percent accuracy on *Driver* testing decreased from that before an on-call night to that after being on call, with a significant deterioration in performance ($P<.01$). The improvement from testing after an on-call night to the recovery at rest was significant ($P<.03$). There was no change from the initial test to recovery on the percentage scores. On the raw score data, which included accuracy plus speed of response, the deterioration from before to after on-call testing was significant ($P<.05$). The improvement from the post-on-call test results to the results after recovery was significant ($P<.0005$). As the graph shows (Figure 1), there is a significant improvement in the third performance results under rested conditions from those of the first test under rested conditions ($P<.004$).

Rapid Number Comparison testing showed a significant deterioration under post-on-call conditions ($P<.005$). Improvement after sleeping was also significant ($P<.0001$). There was no significant change from the first test under rested conditions to the final control test under rested conditions (Figure 2).

Concentration testing showed a deterioration in the results under post-on-call conditions significant to the P less than .05 level. There was significant improvement after rest compared with the post-on-call conditions ($P<.0001$). There was significant improvement from the rested recovery test results compared with those of the baseline test ($P<.003$) (Figure 3).

There was an incremental improvement with each at-

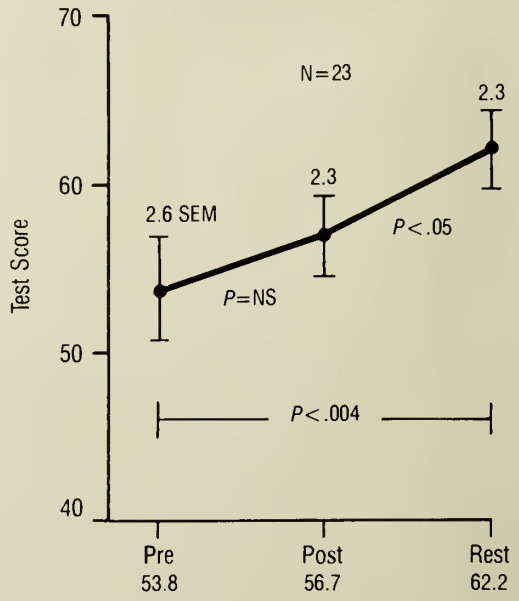

Figure 4.—The graph shows performance results on the *Math Problems* test when given before (Pre) and after (Post) being on call and when rested (Rest). NS = not significant, SEM = standard error of the mean

tempt in *Math Problems,* but this trend was not statistically significant. There was improvement in the results from the third test under rested conditions compared with after being on call, which was significant ($P<.05$). The initial test results compared with those of the third test under rested conditions did show significant improvement ($P<.004$) (Figure 4).

An attempt was made to identify specific factors that would predict deteriorating performance when sleep deprived. No significant correlation could be identified between change in performance and hours of sleep obtained on call, total hours awake, age, sex, or year in training and hospital rotation of subjects.

Discussion

Several factors included in the design of this study minimize its likelihood of demonstrating a statistically significant deterioration on these cognitive tests. First, the possible effect of practice or learning on these tests decreases the difficulty of the post-on-call test. The effect of learning can be present both in the familiarity with the test and with increasing dexterity in manipulating the microcomputer keyboard. Tests did not vary, the mathematic problems were identical at each test, and residents learned various shortcuts available in maneuvering the cursor. It is likely that learning played some role in the scoring on these tests. The degree to which this may have modified the results cannot be estimated, but it would serve to minimize the effect of sleep deprivation on performance because each successive test period should show some improvement purely from learning. Certainly, learning may best explain the improvement seen under the rested conditions as compared with the results on the preliminary rested tests.

Second, there was an inherent bias in the subjects who participated and completed the test. Of the initial 31 subjects who participated in the baseline study, 5 did not complete the study because they said they were too tired. Therefore, the results are modified by including only those residents who were moderately fatigued but still able and willing to participate and complete the study. Those most exhausted were self-excluded.

Third, assistance was given on one test to those too fatigued to complete the test on their own. In summary, all possible controllable factors in the design of the study were set to work against the hypothesis that cognitive performance would deteriorate after sleep deprivation.

Various studies have shown a deterioration in performance when sleep is limited to less than three[6] to five[16,17] hours a night. Our experience from this institution and at other teaching hospitals is that house staff rarely get more than three hours of sleep per night when on call.

Previous literature has also shown that the more complex the task, the greater the deterioration likely to be evident under conditions of sleep deprivation.[4] Similarly, the greater the time required to complete the test, the more likely deterioration would be evident. A commonly stated period of time for testing before which deterioration is less likely to be evident is about three minutes.[4] This is supported by the results of this study, which showed deterioration in the three more complex tasks presented by the *Driver, Concentration,* and *Rapid Number Comparison* tests. The simple *Math Problems* required testing periods of less than a minute each. This test showed no statistically significant deterioration under post-on-call conditions.

Research has also shown that visual vigilance is one of the more highly sensitive areas to show deterioration in performance following sleep deprivation. This was confirmed in our tests showing greater deterioration in rapid number recognition.[4,7,9] Other studies have shown that impairment in task performance following sleep deprivation persists the day following sleep.[18] Residents who routinely go without substantial sleep every third or fourth night still showed significant deterioration.

A question could be raised as to whether the residents had a "secondary gain" in demonstrating deterioration after being on call and therefore might not give an optimal performance on the post-on-call test. As with pulmonary function tests, it is extremely difficult to reproduce suboptimal results in a consistent manner on these tests. The high degree of correlation on repeat testing in all three sessions argues against less-than-maximal performance. Furthermore, residents are generally highly motivated to provide the best services for the patients entrusted to their care. To suggest less than optimal effort would be consistent with emotional imbalance reported elsewhere.[3,7,8] That this imbalance would have its effects on the entire subject population would add further evidence to the detrimental effects of sleep deprivation on house-staff affect during on-call nights.

Internal medicine residents even on an every-fourth-night schedule may suffer from chronic sleep deprivation. If this is the case, this study would have a decreased likelihood of showing significant results. Any decrement in baseline, control function should have decreased the divergence between the sleep-deprived and control periods. Had the subjects been completely well rested, such as from no sleep deprivation for months, we could assume that results would have shown more notable differences in performance.

No actual norms exist for the tests used. They are not intended to test actual function but rather an improvement or deterioration in individual function. Previous studies have looked at physicians' ability to perform specific medical tasks.[9] The strength of this battery of tests is that it tests more global functioning in sleep-deprived medical house officers. The more complex tasks showed greater deterioration than the simple tasks. Hand-eye coordination and the ability to process complex data were more affected than simple tasks.

An argument can be made that this study did not directly assess medical skills such as placing arterial lines, interpreting blood gas measurements, or making rapid diagnoses. The various tests assessed cognitive function ranging from reaction time and eye-hand coordination to attention span and rapid numeric discrimination, which has direct implications on those skills required of practicing physicians. We chose to use standardized cognitive tests to elicit and detect a change in psychomotor and cognitive functions. That the duties and responsibilities of direct patient care require far more complex cognitive functions than these tests can hope to assess cannot be denied. The deterioration evident in these tests may therefore be moderate relative to the actual effects sleep-deprived conditions may have on cognitive tasks required for direct patient care.

This study showed a deterioration in performance in cognitive testing after periods of short-term sleep deprivation—that is, on-call nights—that are standard in many training

programs. If further studies confirm this relationship between sleep deprivation and a decline in cognitive performance, this may have medicolegal implications for patient care under conditions where house staff are deprived of normal sleep. Training programs are going to have to change. This study confirms what common sense assumes: house staff perform considerably less well after sleep deprivation. The occupational hazard of prolonged sleep deprivation may also have further implications for residents in house-staff training programs who drive home after an on-call night. Given the results of this study, we are concerned about ensuring optimal patient care and resident safety after a sleepless, stressful night on call.

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Perceived Health Quackery Use Among Patients

A Physician Survey

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HEALTH QUACKERY in this country is recognized as a major problem. In 1983, the United States Senate Special Committee on Aging cited medical-related fraud as the most harmful type of fraud directed against the elderly.[1] In the *1984 Report by the Subcommittee on Health and Long-Term Care* of the US House of Representatives Select Committee on Aging, it was estimated that health quackery to the elderly cost $10 billion.[2] The cost of health quackery to the American public is estimated to be $26 billion annually.[3] In addition to the financial loss, patients who turn to dubious methods of treatment may delay or forsake regular medical care and thus may lose valuable time in obtaining early diagnoses and treatment; furthermore, some fraudulent therapies can cause direct physical harm.[4-7]

To assess the extent of the quackery problem as perceived by the local medical community and the willingness to become involved in antiquackery efforts, a mail survey was conducted among San Bernardino County Medical Society physician members. The survey focused on the use of dubious health remedies by patients.

Methods

The survey was conducted by mail under the direction of the San Bernardino County Public Health Department's Nutrition Quackery Prevention Program in cooperation with the San Bernardino County Medical Society. The questionnaire was mailed to 942 active members of the San Bernardino County Medical Society. In an attempt to reach nonrespondents, a follow-up mailing was conducted approximately two months after the initial one.

In the survey, physicians were asked the following: their opinions concerning the extent of health quackery as a problem; known patient use of health quackery treatments for cancer or other medical conditions; education concerning health quackery; willingness to attend a health quackery course; willingness to distribute health-quackery prevention literature to patients; and reporting of cases of suspected fraud. Because of the number and variety of fraudulent treatments available for cancer, questions were presented in two sections, one dealing exclusively with cancer and the second covering other medical conditions.

The US House of Representatives' report defined a quack as ". . . anyone who promotes medical schemes or remedies known to be false, or which are unproven for a profit."[2] For the purpose of this survey, which focused on patient use, the following definition of health quackery was provided to assure that all respondents would have a similar understanding of the term:

> Health quackery is the use of certain drugs, diets, devices, food supplements, and techniques not approved by the medical community that if taken or used as a treatment for a disease condition may cause harm to the patient or, at best, have no beneficial or curative effect.

Results

Questionnaires from two mailings were returned by 429 physicians, for a response rate of 45.5%. Of the 429 responses, 12 were excluded from analysis because physicians, such as pathologists with no patient contact, had indicated that the survey was not relevant to their practices. Responses were, therefore, analyzed for 417 questionnaires.

Most respondents (89.9%) indicated that they were attending physicians. The remaining consisted of 1 intern, 1 resident, and 40 physicians who did not check any physician category.

All but 31 physicians indicated an area of specialization, with 20% specializing in internal medicine, 16% in family practice, 7% in surgery, 7% in obstetrics and gynecology, 6% in pediatrics, 5% in psychiatry, 3% in oncology, and the others in various other fields.

Half the physicians surveyed (51%) indicated that they considered health quackery a major problem; 48% viewed it as a minor problem; 1% thought there was no problem or gave no answer.

Of those responding, 41 (9.8%) said they had taken a course in health quackery prevention; the remaining 90.2% had not. Of the physicians who had received health-quackery prevention education, 24 had taken a continuing medical education course on this topic, 13 had studied health quackery as part of their standard medical training, 3 had attended other types of courses or seminars, and 1 did not specify the type of health quackery education received.

Of physicians who responded, 58% indicated that they would take a health-quackery prevention course if one were offered locally, and 82% would distribute health-quackery prevention literature to their patients.

Of the 417 physicians, 293 (70%) had at some point encountered a patient who reported using health quackery products or services for a medical condition. Most physicians in all specialties except radiology, rheumatology, and neurosurgery had had such patients in their practice. All 13 oncologists surveyed had encountered a patient who had used some form of cancer quackery treatment. Patient use of quackery products or services was reported by 83% of internists and 77% of family practice physicians (Table 1).

(Nishiwaki R, Morton A, Bouchard C, et al: Perceived health quackery use among patients—A physician survey. West J Med 1990 Jan; 152:87-89)

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Patients used health quackery products or services mos' often for cancer. Quackery related to cancer was reported by 200 physicians (48%). The types of cancer specified most often were breast, colorectal, and cancers of the lung, uterus, and skin. Of the 200 physicians whose patients had used cancer quackery, 179 specified at least one treatment category. Quackery treatments of cancer most often involved unapproved drugs (35%), food supplements (28%), and special diets (26%). Of physicians whose patients had used bogus cancer treatments, 98 (49%) reported having a patient who had rejected medical treatment in favor of quackery.

Of those responding to our survey, 231 physicians reported having patients who used quackery treatments for conditions other than cancer, including arthritis (106), obesity (91), and heart disease (63) (Table 2). Quackery for these conditions consisted of the use of unapproved drugs (29%), food supplements (28%), and special diets (26%). Of physicians surveyed, 44% who had encountered bogus treatment of conditions other than for cancer reported having a patient who had rejected standard medical treatment in favor of quackery.

Of the 293 physicians who knew about patient use of quackery for any condition, 20 (6.8%) had reported the nonstandard treatment to appropriate agencies. Of the 200 physicians encountering cancer quackery, 167 did not report it to an authority. The four most common reasons for not reporting medical fraud were uncertainty about where to file a report, a lack of faith in agencies' effectiveness in dealing with the problem, a concern about possible litigation, and insufficient time to report.

TABLE 1.—*Physicians With Patients Who Had Used Health Quackery Treatment*

Physician Specialty	*Yes*	*%*	*No*	*%*	*Total*	*% of Respondents*
Internal medicine	69	83.1	14	16.9	83	19.9
Family practice	51	77.3	15	22.7	66	15.8
Surgery	22	73.3	8	26.7	30	7.2
Not stated	20	64.5	11	35.5	31	7.4
Obstetrics and gynecology	17	54.8	14	45.2	31	7.4
Pediatrics	14	56.0	11	44.0	25	6.0
Oncology	13	100.0	0	0.0	13	3.1
Anesthesiology	12	66.7	6	33.3	18	4.3
Psychiatry	11	57.9	8	42.1	19	4.6
Orthopedics	10	62.5	6	37.5	16	3.8
Ophthalmology	10	66.7	5	33.3	15	3.6
Emergency medicine	6	100.0	0	0.0	6	1.4
Urology	5	83.3	1	16.7	6	1.4
Dermatology	5	100.0	0	0.0	5	1.2
Otolaryngology	5	62.5	3	37.5	8	1.9
Pathology	4	50.0	4	50.0	8	1.9
Radiology	4	30.8	9	69.2	13	3.1
Cardiology	3	60.0	2	40.0	5	1.2
Pulmonary medicine	2	100.0	0	0.0	2	0.5
Neurosurgery	2	40.0	3	60.0	5	1.2
Neurology	2	50.0	2	50.0	4	1.0
Allergy	1	100.0	0	0.0	1	0.2
Nephrology	1	100.0	0	0.0	1	0.2
Nuclear medicine	1	100.0	0	0.0	1	0.2
Physical medicine	1	50.0	1	50.0	2	0.5
Diabetes and endocrinology	1	100.0	0	0.0	1	0.2
Geriatrics	1	100.0	0	0.0	1	0.2
Rheumatology	0	0.0	1	100.0	1	0.2
Total	293	70.3	124	29.7	417	100.0

Respondents who had discovered and reported medical fraud stated that they had submitted reports to a state board of medical quality assurance (5), a county health department (2), or other agencies and persons. Of the 20 physicians who had reported quackery, only 7 did so to agencies charged with investigating or prosecuting such cases.

Discussion

Although our survey data reflect that most physicians have encountered patients using unorthodox products and services, it is interesting to note that many physicians had not taken health-quackery prevention courses as part of their medical training or subsequent continuing medical education. This fact, coupled with the expressed willingness to take courses and to distribute materials about quackery prevention to patients, points to the need for increased efforts in these areas. Physicians should be provided more education regarding health fraud and should regularly peruse such publications as the *National Council Against Health Fraud Newsletter, Environmental Nutrition, Nutrition Forum,* and the *American Council on Science and Health Newsletter.*

The lack of health quackery reporting found in this survey is a major concern. The medical community should

TABLE 2.—*Quackery by Medical Condition*

Condition	*No. Physicians Listing Conditions*
Cancer	200
Arthritis	106
Obesity	91
Heart disease	63
Asthma	9
Mental illness	8
Back pain or pain	7
Anxiety	7
Multiple sclerosis	6
(Peripheral) vascular disease	5
Infection	5
Gastrointestinal disease	4
Eye diseases	4
Abdominal pain	4
Diabetes mellitus	3
Behavior problems	2
General health maintenance, diet fads	2
Urinary diseases	2
Condition not stated	2
Hypertension	1
Allergies	1
Cerebral infarcts	1
AIDS	1
Poor vision	1
Pancreatitis	1
COPD	1
Emphysema	1
Abscess	1
Tumor	1
Vaginal bleeding	1
Ovary	1
Fracture of foot	1
ASVD	1
Kidney disease	1
Seizures	1
Total	546

AIOS=acquired immunodeficiency syndrome, ASVO=atherosclerotic vascular disease, COPD=chronic obstructive pulmonary disease

TABLE 3.—*Where to Report Health Fraud*

Problem	*Filing a Complaint*	*Regulatory Agency to Contact**
Drug or device marketed with false or exaggerated claims	Elected representatives	Health Fraud Branch, Food and Drug Administration (FDA), 5600 Fishers Lane, Rockville, MD 20857 State attorney general Regional FDA office Local district attorney State food and drug branch State board of pharmacy
Phony mail-order promotion	Editor or station manager of media outlet where ad appeared	Chief Postal Inspector, US Postal Service, Washington, DC 20260 Local postal inspector
Improper treatment by licensed practitioner	Local professional society or organization (if practitioner belongs) Local hospital (if practitioner is on staff)	State licensing board Private attorney for possible lawsuit
Improper treatment by unlicensed person		Local district attorney State attorney general State licensing board Private attorney for possible lawsuit
False advertising	Local Better Business Bureau National Advertising Division, National Council of Better Business Bureaus, 845 Third Avenue, New York, NY 10022 Editor or station manager of media outlet where ad appeared	Bureau of Consumer Protection, Federal Trade Commission (FTC), Washington, DC 20580 Regional FTC office Local district attorney Private attorney

*Where more than one agency might be interested, report to all of them.

strongly encourage quackery victims to demand action of regulatory agencies. Without health care practitioners documenting and reporting harm, little will be done by agencies charged with controlling this problem. Physicians, dietitians, nurses, and other health care personnel should be trained to identify which cases are appropriate to report and where to report them (Table 3). For information and advice about questionable products or services, one may contact the National Council Against Health Fraud, Inc, PO Box 1276, Loma Linda, CA 92354.

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Lessons From the Practice

After Shock

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Heading home after an afternoon of meetings for a cancer prevention project that I'm helping organize for the West Oakland community, I was about a block from the Cypress overpass of I-880 when the October 1989 earthquake hit and, after steering clear of falling electrical wires, found myself at the foot of the crumpled freeway. I wish I could say that, being a physician, I then leaped into action, but for a dazed moment I first considered trying to continue on my way. Luckily, the sight of people from the ghetto houses and industrial yards charging into the rubble to look for victims awakened me, and I grabbed my stethoscope—the only medical equipment I routinely carry—and ran to the closest fallen vehicle, a semi-trailer truck that evidently had tumbled from the upper deck of the freeway. The trucker inside looked dead. I heard no breath sounds but did detect a pulse—which seconds later dwindled and stopped. I considered doing cardiopulmonary resuscitation but knew I should move on to those still alive. I tried organizing some onlookers to assist me but found them too stunned to be of use. I felt desperate and alone, buoyed only by the thought that medical disaster teams would soon arrive.

Some minutes later, I was joined by a paramedic in full uniform, and I felt great relief—as if the cavalry had finally arrived. But there was no one with her (she'd come from home), and, looking around me—seeing so many crushed cars and hearing victims screaming—I felt overwhelmed by the enormity of the situation. A numbness set in, followed by terror, when a clearly in-shock television newsman (a well-known anchorman who had somehow found his way to the disaster scene long before other reporters) asked me if I had seen his camera crew—and I noticed that, during the scoop of his career, the note pad in his hands was completely blank.

When medical and rescue workers finally arrived, I identified myself as a physician and was presented with a patient making ominous gurgling sounds who required intubation that, once accomplished (by a paramedic), allowed her to be taken off by ambulance. I expected an onslaught of similarly critical patients and set about developing a curbside medical station, including hanging IVs from the lower rung of a telephone pole. But, after 20 or so minutes, I hadn't seen a single patient—they were trapped above. When a paramedic on the lower deck called down for help with starting IVs, I decided to go up.

I climbed a thin, wobbly ladder and crawled in under the collapsed upper deck. There were maybe four feet of headroom, and, a few feet away, eight or so rescue workers were huddled in the darkness over two young women whose lower legs were pinned under their crushed dashboard. The women were conscious, able to speak, and had no obvious internal injuries. Intravenous infusions were started on them, and the fire department personnel went to work with the "jaws of life." But things went frustratingly slowly, with crescendos of chaos as everyone yelled out ideas of what should be done. One paramedic was in such emotional shock that he was becoming psychotic—seeing amputated limbs that were actually intact. He soon had to be removed from the scene. And he wasn't the only one with mistaken visions.

Earlier a paramedic had told me that she'd heard over her walkie-talkie that San Francisco, San Jose, and Sacramento had been hit just as hard as Oakland, and that the Bay Bridge was down. In my mind, hundreds of thousands of people were dead, a "fact" I now erroneously confirmed for myself by gazing out through a crack and sighting what I thought were Bay Bridge towers without spans between them—that they had all fallen into the Bay. I told my fellow rescuers what I had seen, and they looked out and saw it, too. Only later did I realize I had mistaken tall cranes in the Alameda shipyards for bridge towers.

Fortunately, I began to come to my senses. After the less entangled of the two women was freed, I saw a paramedic do something that I'd thus far completely forgotten (but so had every other health professional I'd seen at the disaster): take a blood pressure, an act so fundamental that even a medical student would think to do it. If the blood pressure was normal, IVs wouldn't be as necessary, and they'd been repeatedly kinking up and pulling out, forcing us to step back in the way of the emergency personnel to restart them. I grabbed the blood pressure cuff and went to the remaining trapped woman and took her blood pressure. It was completely normal (120/80, with a pulse rate of about 80). I made sure that there were no obvious signs of internal or external bleeding and then announced to the group that we medical personnel should forget about keeping an IV going, step back, and let the fire department personnel do their job. And it worked; a semblance of organization set in. Information, I realized, is the treatment for chaos.

When the remaining woman was freed, we got her down to a waiting ambulance, which then went nowhere—awaiting orders on where to take her. This confused me, because I thought that the only trauma center in Oakland was at Highland General Hospital and that she'd be immediately taken there. I reasoned, however, that there were too many cases for them to handle. (I heard later that they only saw a handful of trauma cases; lacking emergency power to run their x-ray machines, they were on "divert.")

It had now been over four hours since the quake. I couldn't see any rescue activity where I was, so I headed back up the street to where my car was. Evidently, the very

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people who had been the major rescuers, the community people, were now cordoned behind barricades a block away. Up ahead, bright portable lights were shining on a squadron of physicians, most of them dressed in clean green surgical scrubs, one even wearing paper shoe covers. There was an array of guerneys and sophisticated medical equipment. It turned out they were a trauma team from Highland, had been there for about two hours, and had yet to see a patient. This deeply disturbed me; the women we'd just gotten out should have been brought up here for immediate and definitive trauma care, but there was apparently little, if any, communication and coordination of the overall rescue operation.

Feeling too weary to continue, I retreated to my car, turned on the radio, and discovered, to my amazement, that I'd just happened to be in the worst of the disaster sites (but hadn't known it), and that hundreds of thousands of people weren't dead! My joy was short-lived, though, as I reflected on the reality of the situation: in the face of this relatively small-league earthquake (not the "Great Quake"), I, along with most of the other medical and rescue workers, had gone into varying degrees of shock—and functioned accordingly—as had, apparently, the civil disaster plan for the region.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
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Series' Editors

Lessons From the Practice

My Favorite Patients Are on Medicaid

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Two of my favorite patients died this past week. Sharon was truly inspiring. Crippled when an infant with spinal muscular atrophy, she lived 44 years with profound muscle weakness. Ten years ago she asked me to become her physician. With Harrington rods in her back and chronically infected staghorn calculi in her kidneys, she was a complex patient with many management problems. These were more than offset by her cheerful manner and the sight of the flowers she placed on the post of her electric wheelchair.

Seven years ago she announced her marriage to Michael, a young man with Marfan syndrome who also became my regular patient. Six years ago she caused me great alarm by becoming pregnant. Near term, Sharon developed respiratory failure and required an emergency cesarean section that produced a normal little girl called Sara.

Subsequently, Sharon developed breast cancer in both breasts a year apart. Her chronic urinary infections and occasional sepsis led to an attempted lithotripsy for multiple renal stones. All of this kept Sharon and me close over the last five years. She died peacefully with congestive heart failure and metastatic cancer, and now I look forward to the future with Michael and Sara.

Evelyn, at the age of 80, moved from the city to live with her daughter in our small town. Weighing more than 200 pounds, and with blood sugar levels over 250 despite lots of insulin, she became my first patient every third Tuesday morning. During our first seven years together, she required only one hospital stay despite developing congestive heart failure and recurring arrhythmias. A year ago Evelyn had a major stroke that confined her to bed for the rest of her life. What her daughter Lola and I expected to be a few more months of life turned out to be a year of regular home visits. She lost over 100 pounds but never her smile when I came to visit. With counseling, Lola was able to give her a peaceful death at home.

As I reflect on the care and passing of these two special patients, it occurs to me that they were both on Medicaid. If our office policy had been not to accept Medicaid patients—as it is for most physicians in the county—I would have been deprived of caring for Sharon and Evelyn.

I practice with four other family physicians in a rural town of 10,000 people. We have an open door policy to care for all segments of our community, and about 15% to 20% of our patients are on Medicaid. Most of them, and most of our other patients, are considerate and sensitive human beings in need of health care. Yes, Medicaid reimbursement barely covers office overhead, and yes, we would each earn about $10,000 a year more if all our patients were fully insured, but we make a good living. What my general practitioner uncle taught me is true: with low income patients, I will do the most good and derive the most satisfaction.

Unfortunately, even our openness to Medicaid patients has limits. Two neighboring communities of 35,000 each have lots of physicians, yet almost none of the primary care physicians in these two towns will accept new Medicaid patients. As requests for care from Medicaid patients in these communities increased, we knew that we would soon have a much higher percentage of these patients and that the economics of our practice would suffer. In order not to be overwhelmed, we chose not to accept out-of-town Medicaid patients.

Our ambivalence with Medicaid increased last year when we opened a satellite clinic in one of these larger towns. If we were the only primary care practice accepting Medicaid, a disproportionately high number of Medicaid patients would seek our care, and the practice would suffer financially. Accepting a certain percentage of Medicaid patients would have us still rejecting many. We compromised by accepting new obstetrical patients on Medicaid and their families.

Our county is generally prosperous, and only 15% of the population is on Medicaid. If everyone accepted these patients proportionate to the population, no one would be overwhelmed, and all our practices would still be successful. This idea has been discussed and even tried halfheartedly over the years, but each new frustration from the Medicaid payment system seems to squash whatever altruism exists. Yesterday, a community activist called to propose that through the county medical society, we all try it again. A petition will be passed around asking all practices to accept up to 15% Medicaid patients. I think about how much richer our practices will be if we do.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Series' Editors

(Scherger JE: My favorite patients are on Medicaid. West J Med 1990 Jan; 152:92)

From the Department of Family Practice, University of California, Davis, School of Medicine, Davis, California.

Reprint requests to Joseph E. Scherger, MD, Predoctoral Education Program, Department of Family Practice, TB 152, University of California, Davis, School of Medicine, Davis, CA 95616.

Radiologic Case

Left Hilar Mass Without Pulmonary Disease

MARK G. STEPHENS, *Tucson, and* JONATHAN M. LEVY, MD, *Scottsdale, Arizona*

A "Radiologic Case" is published in this format on a regular basis. Physicians interested in contributing to the series are encouraged to send their radiologic cases to the series' editor.

JONATHAN M. LEVY, MD
Series' Editor

A 50-year-old man scheduled for an arthroscopy of the knee had a preoperative chest film that showed the left hilum to be markedly enlarged (Figure 1). He was in excellent health, except for pain and locking of the left knee. Because of the findings on the chest x-ray film, a further diagnostic test was done.

What is the differential diagnosis?

Which imaging test would you do next?

SEE FOLLOWING PAGE FOR DIAGNOSIS AND DISCUSSION

Figure 1.—A preoperative chest film shows a greatly enlarged left hilum.

(Stephens MG, Levy JM: Left hilar mass without pulmonary disease. West J Med 1990 Jan; 152:93-94)

Mr Stephens is a fourth-year premedical student at Arizona State University, Tucson. From the Department of Diagnostic Radiology, Scottsdale Memorial Hospital, Scottsdale, Arizona (Dr Levy).

Reprint requests to Jonathan M. Levy, MD, Department of Diagnostic Radiology, Scottsdale Memorial Hospital, 7400 E Osborn Rd, Scottsdale, AZ 85251.

DIAGNOSIS: Pulmonary artery aneurysm

CHEST X-RAY FILMS are the most common radiologic examination done in the United States. A large proportion of these films are taken as part of a routine physical examination or before surgical procedures. Though the yield of these examinations in asymptomatic patients is low, important lesions are occasionally found. In this patient, the left hilum is greatly enlarged (Figure 1). There is no right hilar mass or pulmonary disease.

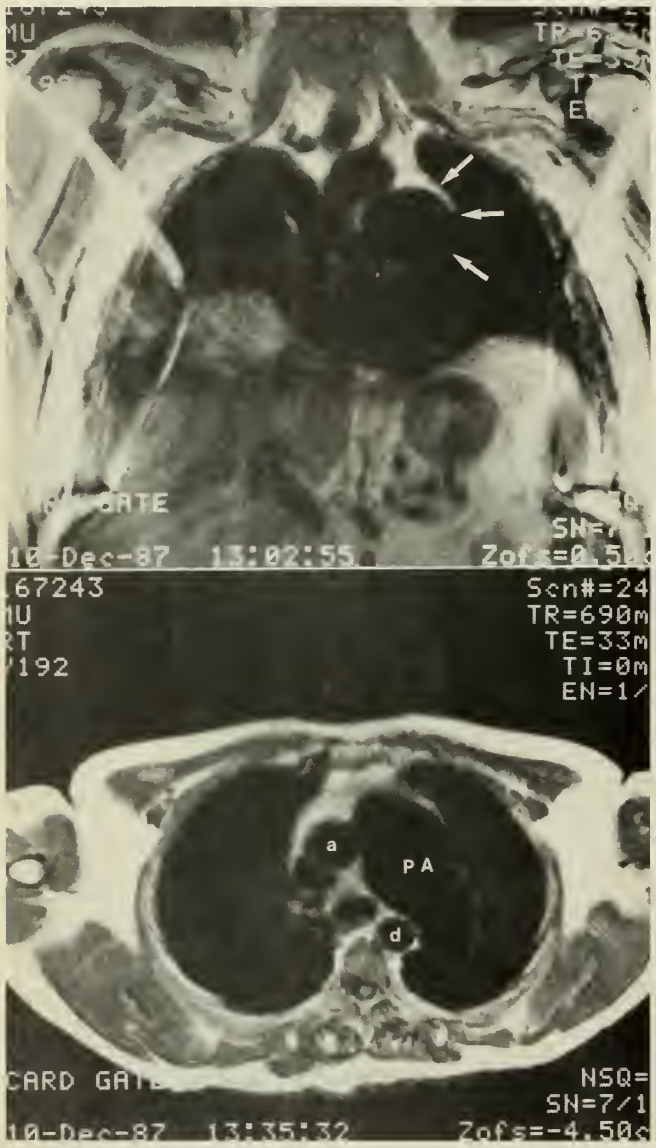

Figure 2.—Top, A coronal magnetic resonance imaging scan shows a "hollow" mass in the position of the left main pulmonary artery **(arrows). Bottom,** An axial scan shows a lobulated appearance of the mass **(PA)** due to branching of the pulmonary artery. Note also the ascending **(a)** and descending **(d)** thoracic aorta.

The differential diagnosis of hilar masses includes primary and secondary neoplasm, adenopathy due to inflammatory disease, sarcoidosis, and vascular masses. Once an abnormality is found, further examinations have the goal of characterizing the exact nature and, if necessary, the resectability of the lesion. In the past, plain film tomography, computed tomographic scanning, angiography, and nuclear medicine have been used for this purpose. Magnetic resonance imaging (MRI) offers a new and often better window into the differential diagnosis of hilar masses, as seen in this case.

The use of MRI for the diagnosis of hilar masses is based on the exquisite ability of the technique to resolve small differences in tissue density. This allows an accurate assessment of fat planes, density of the mass, and extent of disease. Another important characteristic is that flowing blood produces a signal void (black image) on MRI. This is because the process measures protons that have been "excited" by radio-frequency pulses. During the period between excitation and measurement, blood flow causes these protons to move away from the field to be replaced by "unexcited" protons, which have no signal. Our patient's mass is "hollow" because it contains flowing blood (Figure 2) and is in the anatomic position of the main pulmonary artery. It therefore represents a pulmonary artery aneurysm.

Pulmonary artery aneurysm is an uncommon disorder, and idiopathic lesions are particularly rare. Most aneurysms are caused by other processes: poststenotic dilatation from valvular pulmonic stenosis; pulmonary hypertension due to mitral valve disease, patent ductus, or atrial or ventricular septal defect; or cystic medial necrosis in Marfan's syndrome. Sudden death has been described in as many as a third of patients with pulmonary artery aneurysms. This is usually caused by dissection with rupture into the pericardium or bronchus. Most patients have pulmonary hypertension, which causes such symptoms as hemoptysis, dyspnea, or chest pain. Occasionally patients are asymptomatic when the abnormality is found. Aneurysms are more common on the left than on the right.

The treatment of pulmonary artery aneurysm is surgical, with grafting or direct repair if possible. Our patient is currently being evaluated for surgery.

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Medicine in Society

Who Are You?

GARY G. KARDOS, MD, *San Francisco*

Toward the end of a workday, while I was examining one of my patients, her 4-year-old son asked, "Who are you?" Although my answer was simple, it later struck me that this question is worthy of more serious consideration.

On the demographic level a physician is a person with 20 years of formal education, specialized training, and a bare minimum of a year of postgraduate education who possesses a Physician and Surgeon Certificate entitling him or her to practice medicine.

On the regulatory level a physician is granted a license to practice by a state regulatory agency if he or she provides this agency with proof of a diploma of Doctor of Medicine, evidence of satisfactory completion of at least a year of postgraduate education, and is able to pass a written licensing examination. Physicians remain under review of their professional activities, mental and physical health, and annual fulfillment of continuing postgraduate educational activities, and they are also subject to careful scrutiny for any deviations in competency or conduct that are brought to the attention of a state board. In addition, any malpractice settlement in excess of $30,000 is reportable (at least in California) to the state board of medical examiners. Any report or complaint by the public, peers, or others is investigated and may become the basis for a restriction to or even a revocation of this license.

These control mechanisms are the price physicians pay for the societal trust in granting them licenses to practice medicine. So it should be.

On the professional level a physician has undergone the scrutiny of his or her professors during medical school years and teachers and attending physicians during postgraduate training, as well as both written and oral examinations. After these rites of passage are completed, each hospital medical staff to whom a physician applies for hospital privileges carefully examines the credentials of the applicant; and after acceptance, a physician's competency and physical and mental health are subject to ongoing review.

Acceptance by one's colleagues is a complex phenomenon and encompasses far more than mere technical competence. It includes personality, an ability to get along, acceptance of the community practices and standards, and the avoiding of too much windmill tilting. Should this last be evident from the very start, the labels of strange, difficult, egotistical, and the like rapidly become known, and success in practice is far less likely. In simple terms, the community of practicing physicians has habits, customs, and standards. The practice of medicine is a game with some written and some unwritten rules that have to be discovered quickly if one wishes to participate.

At the hospital level peer review of patient admissions, discharges, complications, and deaths is ongoing. If substantial deviations from professional standards of competency and character are discovered, corrective action may begin. Fair hearings with due process occupy a tremendous amount of medical staff leaders' time. Peer review protection is a complicated issue, and I can merely note that there are disquieting problems related to antitrust charges and the balancing act between the individual physician's rights and those of the profession and society as a whole.

On the economic level today's physicians are accused of charging too much, earning too much, acting too businesslike, and lacking in humanity. There are too many specialists and not enough family practitioners, and there is a maldistribution of physicians, with too many congregating in urban areas. In such areas, intense competition and lack of patient volume are alleged to encourage physicians to recycle patients excessively, order more tests (especially if there is economic gain involved), and suggest more procedures, all to keep up the dollar flow. Although the percentage of physicians who actually do this is low, the public's and third-party payers' perception is that the opposite is true. Today physicians' voices tend to fall on deaf ears. Even when their reasons are completely altruistic, their recommendations are viewed with suspicion and distrust.

On the moral level a physician's primary goal of beneficence encounters the current, almost singular, focus on patient autonomy. The complexities of modern medical care have geometrically increased and with this has come increasing attention to values relating to health and disease. Everyone is in the act, to the detriment of the physician-patient relationship. All major moral theories, utilitarian, deontologic, and justice-based, fail to address analytically the resolution of values in conflict. At best, these theories give methodology to ethical analysis but not answers. Legal rulings in the United States have focused on competent individual autonomy, but this does not make such singular focus ethically proper.

Two well-known ethicists, Joseph Fletcher, PhD, and David C. Thomasma, PhD, have called attention to the need to interpret values from within the physician-patient relationship. According to Thomasma, a moral model based on physician conscience that acknowledges the ethical issues for physicians, recognizes the need to preserve as many patient values as possible, and understands the need for a healthy respect for moral ambiguity seems far more appropriate than the present norm.[1] There are biologic norms within medicine. The ethical conduct of physicians needs to be interpreted in terms of these norms, concurrently recognizing

(Kardos GG: Who are you? West J Med 1990 Jan; 152:95-96)

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patient vulnerability, patient wishes, and the sharing of relevant information. In addition, physicians must use their skills and implied power wisely and with great integrity.

From a philosophical viewpoint, truly informed consent is not achievable, regardless of what attorneys say or wish. The impact of disease on individual autonomy is neither addressed properly nor understood by either legislators or many ethicists.

In other words, the playing field between physician and patient is never level: patients are more vulnerable and physicians are held to much higher standards of integrity and must recognize explicitly the advantage specialized knowledge gives. In the final analysis, the success or failure of this unique relationship begins and ends with trust.

On the personal level who are we? Granting that each of us has an image of what being a physician represents and what image he or she wishes others to have, are there any common threads that link one physician to another?

I think that within each of us is an underlying intellectual curiosity about basic biology, its mysteries, and the amazing progress that science has made in defining disease and altering its course. Perhaps it is here that the phrase, sometimes to cure, sometimes to help and always to comfort, is applicable.

There is also an element of altruism, of wanting to work with and help people.

A part of being a physician is theatrical—not in any pejorative sense but rather in the individual physician's manner as one attempts to allay needless fear and convey confidence. This is, after all, a role model that has occupied prime-time television; and to some extent, all physicians are judged at least in part by their bedside manner.

There is another part that, for want of a better term, is called egotistical. So long as this element is recognized, understood, and properly compartmentalized, all is well. Only when such personal conceptions are distorted and the statement, I can do no wrong, is believed will trouble arise. Good physicians have to have reasonable confidence in their abilities to diagnose and to treat.

Each of us must guard against the tendency to become hardened, insensitive, and unresponsive to the amazing frailty and heterogeneity of human illness. When feelings become encased in a thick layer of social concrete, we are called callous and uncaring, and we are also more prone to error because when such personality traits occur, there is a concurrent tendency to be less attentive to detail.

Medicine is a profession that has grown from humble and superstitious beginnings to the scientifically based applied biologic science it is today—along with a degree of uncertainty and unpredictability. As physicians we must respect our origins, our uniqueness, and our responsibilities to the profession and the public, and we must not permit the profession to erode into a trade or business, regardless of the external pressures and forces.

How we will achieve this cannot be predicted with the accuracy of a mathematical column of figures. That we must preserve professional standards and ethics requires daily reemphasis to ourselves, our patients, and to others. This use of the word others is truly intended to be disparaging. The others do not understand what it is to be a physician. I am also certain that many of them do not care to know. But we do. We need to let them know in no uncertain terms by the way we act, by what we do and say, and by continuing to show that we care.

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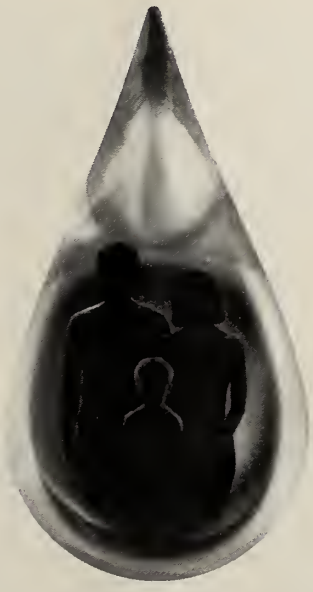

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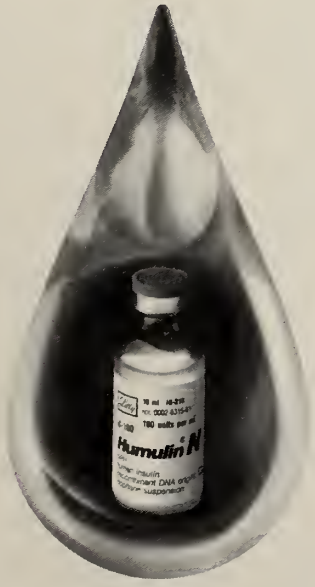

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WANTED: BC/BE FAMILY PRACTICE OR INTERNAL MEDICINE/PEDIATRICS with Emergency Medicine experience for second physician in our Emergency Department. ACLS/ATLS required. Boise offers a variety of cultural activities and is close to skiing, hunting, fishing, white water. Contact Idaho Emergency Physicians with CV at 2312 N. Cole Rd, Ste B, Boise, ID 83704.

SOUTHERN OREGON. BC/BE Family Practitioner to join busy five doctor Family Practice group summer 1990. Practice is located in the Rogue Valley, which is amply endowed with cultural events and outdoor activities. Affordable housing in area of low seismic potential. Admission privileges available at two local hospitals. OB optional. Guaranteed salary and benefits with option to join group after one year. Send CV to Daniel Heyerman, MD, Central Point Medical Group, PC, 524 Manzanita, Central Point, OR 97502.

SALT LAKE CITY, UTAH, FAMILY PRACTICE PHYSICIAN, BC/BE. Excellent opportunity in Salt Lake suburb to join busy practice, near excellent skiing, hunting, and fishing. Our clinic operates six days a week, and our patients are from a growing Salt Lake suburban population. Excellent salary and benefits. A partnership opportunity will be available after two years. Send CV to Robert Davis, MD, Director, Family Medical Center, 1781 W. 90th S., West Jordan, UT 84092; (801) 562-9100.

CARDIOLOGIST. BC/BE sought to join a large hospital based multispecialty clinic. University affiliated residency program. Excellent fringe benefits. Competitive salary. California license required. Send CV to Aung-Win Chiong, MD, The Permanente Medical Group, Inc, 2025 Morse Ave, Sacramento, CA 95825. EOE.

GIG HARBOR, WASHINGTON—INTERNIST. Excellent opportunities in rapidly growing bedroom community for Tacoma and Seattle. Existing medical complex has 19 different health care professionals. Build to suit or finished space available. Information—Dr Jon H. Kvinsland, 5122 Olympic Dr NW, #A201, Gig Harbor, WA 98335; (206) 851-9171.

BC/BE FAMILY MEDICINE/INTERNAL MEDICINE needed for well established, comprehensive clinic in sunny San Diego. English and Spanish a plus. Contact Rhonda Simpson, MD, or Marielena Covarrubias, (619) 234-8171, or send CV to Logan Heights Family Health Center, 1809 National Ave, San Diego, CA 92113. FAX (619) 237-1856.

R2, R3 POSITIONS, INTERNAL MEDICINE, LDS HOSPITAL, SALT LAKE CITY, UTAH

An additional R2 position and R3 position are now open in the Internal Medicine Residency Program at LDS Hospital. LDS Hospital is a 520-bed fully accredited teaching hospital affiliated with the University of Utah Medical Center. This is an excellent opportunity for talented individuals to experience a high quality Internal Medicine program in beautiful Salt Lake City, Utah. Positions available July 1, 1990. Write or contact Shauna Bruun, House Staff Coordinator, LDS Hospital, Eighth Ave and C St, Salt Lake City, UT 84143; (801) 321-1077. Equal Opportunity Employer.

CENTRAL CALIFORNIA. Join our team of Family Practice Physicians in a progressive community health center near Fresno, California. Competitive salary with extra on-call and overtime. Malpractice paid. Generous vacations and time-off policy. Affiliated with UCSF with on-site Family Practice residents and medical students. Varied practice, including Obstetrics, Pediatrics, and in-patient care with an emphasis on health maintenance, patient education, and primary care research. Position is 60 percent clinical, 40 percent teaching. Bilingual English-Spanish helpful. Contact Ardeth Bier, Fresno County Dept of Health, PO Box 11867, Fresno, CA 93775; (209) 445-3353.

ENDOCRINOLOGIST NEEDED to join a busy solo Endocrinologist in a growing southern California city. Established referral base, 300-bed acute care hospital. Competitive salary leading to partnership. Reply with CV to Number 169, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

WYOMING. Wyoming's most desirable town is seeking an ENT Surgeon. Located at the foot of the Big Horn Mountains, and serving an area of 35,000, Sheridan, Wyoming is the town that offers both life-style and opportunity. An up-to-date hospital, combined with a young, specialized medical staff provide the basis for an excellent practice. Contact the ENT Search Committee, 1405 W. 5th St, Sheridan, WY 82801.

SAN FRANCISCO NORTH BAY AREA/NAPA VALLEY. Immediate openings (career and part-time) in a multidiscipline Emergency Department for physicians trained in Emergency Medicine, Internal Medicine, Family Practice, or Pediatrics. Full in-house multispecialty coverage. Complete generous benefit package. Contact Robert Mack, MD, Kaiser Hospital, 975 Sereno Dr, Vallejo, CA 94589; (707) 648-6200. EOE.

DON'T FORGET! The deadline for submitting classifieds for the March issue of WJM is January 25. Send your advertisement to Classified Advertising, WJM, PO Box 7602, San Francisco, CA 94120-7602; or call (415) 541-0900, ext 376.

PHYSICIANS WANTED

UTILIZATION REVIEW POSITIONS

Cost Care, the nation's leading independent utilization management company, is seeking BC physicians to staff the medical services department. These part-time positions will include intensive training in all aspects of health care cost containment including pre-certification, home health care and case management. Prior UR experience is a plus, but not mandatory.

If you are seeking new skills in the changing health care marketplace, please submit your CV to:

Alan R. Greenfield, MD, MBA
Vice President
Medical Services
COST CARE, Inc
17011 Beach Blvd, Ste 400
Huntington Beach, CA 92647

HAWAII. Family Practitioner needed for rural underserved area. Full-time position in nonprofit community health clinic. No OB, hospitalizations optional. Desire dedicated person to work in multicultural setting. Contact Alan Chun, MD, Waianae Coast Comprehensive Health Center, 86-260 Farrington Hwy, Waianae, HI 96792; (808) 696-7081.

INSTITUTION PHYSICIAN needed to staff the Wyoming State Training School in Lander, Wyoming. We have 360 clients in an institutional setting for acute care in an 18-bed health care center. There is a staff of three physicians and one physician's assistant for total medical services. Attractive benefits, no overhead. Pleasant surrounding area including an excellent medical group in Lander. If interested, please contact the Personnel Manager, Wyoming State Training School, 8204 State Highway 789, Lander, WY 82520; or call (307) 332-5302. An Equal Opportunity Employer.

GENERAL INTERNIST/NEUROMUSCULAR/COPD/REHABILITATION. Immediate opening for BC/BE General Internist to join the staff of a 48-bed respiratory unit at an internationally recognized rehabilitation center affiliated with University of Southern California. Management of respiratory-neuromuscular/chest wall disorders, COPD, and tuberculosis. Some critical care. Busy exercise lab. Clinical faculty appointment at USC, depending on qualifications. Interested individuals should send CV to Ahmet Baydur, MD, Chest Medicine Service, Rancho Los Amigos Medical Center, 7601 E. Imperial Hwy, Downey, CA 90242. Equal Opportunity/Affirmative Action Employer.

CALIFORNIA, NORTHERN. Full-time Emergency Medicine staff positions available in 230-bed teaching hospital in Stockton with 50,000 annual visits. Teaching programs in Internal Medicine, General Surgery, Family Practice and Obstetrics/Gynecology. Excellent, prompt specialty back-up. Malpractice, health, and dental provided. Flexible scheduling, $100,000 plus annually. Contact Richard N. Buys, MD, PO Box 1020, Stockton, CA 95201; (209) 468-6818. AA/Equal Opportunity Employer.

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PHYSICIANS WANTED

CALIFORNIA

Primary Care Physicians and Radiologists needed to work as *locum tenens* statewide. High salary, paid malpractice. Work whenever and wherever you wish. Permanent placements as well. **Western Physicians Registry: Northern California, contact Carol Sweig or Jim Ellis, Directors, (415) 673-7676 or (800) 437-7676. Southern California, contact Tracy Zweig, Director, (818) 999-1050 or (800) 635-3175.**

FAMILY PRACTITIONER, NORTHERN CALIFORNIA. Solo Family Practitioner (including OB) seeks BE/BC associate. English/Spanish preferred. Reasonable call. Beautiful "Redwood Empire" town, two hours from San Francisco. Guaranteed salary, benefits. Contact Andrew Coren, MD, 1165 S. Dora, E2, Ukiah, CA 95482; (707) 463-3663.

NORTHERN CALIFORNIA. Enjoy multitude of recreational opportunities. Beautiful Sierras. Easy access to San Francisco. Four Internists seek associate. Growing community in California's gold country. Rural life-style conducive to family life, yet satisfying specialty practice. Robert Hartmann, MD, 815 Court St, Jackson, CA 95642; (209) 223-3837.

ARIZONA. Established Emergency Medicine group has immediate openings for full- or part-time BC/BE physicians seeking career opportunity in busy Emergency Department with excellent location and case mix. Flexible schedules, excellent living and working conditions. Compensation range $150K to $200K for full-time. Send CV in confidence to General Manager, PO Box 80412, Phoenix, AZ 85060-0412.

ONCOLOGIST NEEDED for multispecialty group practice in Seattle; affiliated with University of Washington. Full-time clinical with potential for research. Diverse patient population includes managed care, fee-for-service, retired and active duty military. Attractive salary plus incentive and excellent benefit package. Send CV or contact Mary Anderson, Personnel Representative, Pacific Medical Center, 1200 12th Ave S., Seattle, WA 98144; (206) 326-4111.

GASTROENTEROLOGIST — SAN DIEGO. Thriving multispecialty private practice group seeks Gastroenterologist. The practice offers excellent opportunity to enjoy growing group, see private and managed care patients and build stable future. Compensation includes guarantee plus incentives and benefits. Please send CV to Miriam Stephens Drake, 1450 Frazee Rd, Ste 605-1, San Diego, CA 92108; or call (619) 295-0599.

URGENT CARE/PRIMARY CARE PHYSICIANS for over 90 positions available with various physician groups in Phoenix metropolitan/Tucson, Arizona. Excellent compensation and partnership opportunities. Contact Mitch Young, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

COME LIVE IN THE MOUNTAINS. Internist to share practice/call with three others in attractive small community only 50 miles from Yellowstone National Park. Area abundant in fishing, hunting, hiking, outdoor sports. No state income tax! Generally young, well-trained medical staff with a well-equipped, progressive, newly remodeled hospital. Desire US trained, BC/BE physician, any time between now and summer of 1990. For more information call Ruth McDaniel, CEO, at (307) 578-2489 or send CV to West Park Hospital, 707 Sheridan Ave, Cody, WY 82414. EOE.

RADIOLOGIST. Immediate opening for BC General and Diagnostic Radiologist at teaching hospital near Seattle. Ultrasound, CT, and mammography, plus limited basic angiography and interventional skills. Washington license not required. Regular hours. Full-time or six to nine months per year. Five-year contract. Call Dr Bernstein, (206) 840-9652.

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NORTHERN CALIFORNIA

The Permanente Medical Group, a growing multispecialty group, is recruiting physicians in a variety of specialties for positions throughout our beautiful Northern California region: the San Francisco Bay Area, Sacramento and the Central Valley.

MARTINEZ

Emergency Physicians — Join friendly, relaxed and highly professional colleagues at our 204-bed hospital in the heart of the San Francisco Bay Area. We are seeking experienced physicians, BE/BC preferred. Locum Tenens and part-time work available Summer/Fall, 1989 & Winter/Spring, 1990. Recent adjustments provide excellent hourly rate plus paid malpractice. Career positions also available, providing salary and excellent benefits package. Send CV to: Ted Bayer, M.D., Chief, or Andrea Wagner, M.D., Asst. Chief, Department of Emergency Services, The Permanente Medical Group, Inc., 200 Muir Road, Martinez, CA 94553. (415) 372-1000, ext. 3316 or (415) 372-1124.

Internists and Cardiologist (BC/BE) - Join us in our high quality, expanding, 25 member Department of Medicine where you will benefit from our university affiliated internal medicine residency program. Faculty appointment available. This East Bay suburban setting has excellent schools, and is only 25 miles from San Francisco. Please send CV, or contact Michael Melewicz, M.D., Dept. of Medicine, The Permanente Medical Group, Inc., 200 Muir Road, Martinez, CA 94553. (415) 372-1069.

ROSEVILLE

General Internists (BC/BE) — Immediate openings for California licensed Internists at our Roseville facility, 90 miles from San Francisco or Sierra skiing & camping. University associated residency program. Send CV to: Tony Cantelmi, M.D., The Permanente Medical Group, Inc., 1001 Riverside Blvd., Roseville, CA 95678.

SAN JOSE

Family Practitioner (BC/BE) — Our 228-bed Santa Teresa Medical Center serves 128,000 members. Predominately outpatient practice located in Silicon Valley, approximately 45 minutes south of San Francisco and 30 minutes from the Pacific Coast. Send CV to D. Bardole, The Permanente Medical Group, Inc., 260 International Circle, San Jose, CA 95119.

Surgeons (BC/BE) - One General Surgeon and one Surgeon to do both general and vascular surgery. We are a 9 surgeon department with modern offices adjacent to the 228-bed hospital equipped with 7 operating rooms. We handle a full range of general, thoracic, vascular and plastic surgery cases, and our group includes about 100 fully trained physicians in all specialties. Please apply to the Oakland address below.

SOUTH SAN FRANCISCO

Seeking highly-motivated **BC/BE Internists and a BC/BE Gastroenterologist-Internist** for this expanding practice adjacent to our 125-bed community hospital. Send CV to: Mark Cole, M.D., Dept. of Medicine, The Permanente Medical Group, Inc., 1200 El Camino Real, So. San Francisco, CA 94080.

FAIRFIELD

Excellent opportunity for **BC/BE Family Practitioner** to join a growing department. Multispecialty clinic emphasizing personalized care. Full hospital privileges including ICU/CCU, but no Obstetrics. Very favorable call schedule. Forward CV to: Steven Freedman, M.D., The Permanente Medical Group, Inc., 1550 Gateway Blvd., Fairfield, CA 94533. (707) 427-4260.

Members of our large, multispecialty group earn a highly competitive salary and excellent benefits including scheduled time off, malpractice insurance, medical, dental and life insurance, and a substantial retirement program. Our physicians are free to concentrate on providing quality health care, without the burdens of managing a practice.

To inquire about other openings with our successful, growing medical group, send CV to: Richmond Prescott, M.D., Physician Recruitment Services, Dept. WJM-5114, The Permanente Medical Group, Inc., 1814 Franklin, 4th Floor, Oakland, CA 94612. (415) 987-4949. EOE

KAISER PERMANENTE

Good People. Good Medicine.

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PHYSICIANS WANTED

Join the leader and enjoy your practice!

Family Practice

Pacific Physician Services
A dynamic and growing 65-physician Southern California medical group network, has immediate career opportunities for primary care physicians. Examine our benefits:

- $8K monthly guarantee;
- Monthly FFS productivity incentives;
- Paid malpractice;
- Medical & dental plans;
- Retirement, disability;
- Vacation, CME, sick time.

Discover an enjoyable practice, call

Ruthan Smith
(800) 338-4798
or (714) 825-4401 in CA

SAN FRANCISCO BAY AREA. BE/BC Internist. We currently are seeking highly qualified Internists and subspecialists to complement our energetic Internal Medicine team. Department members provide a full range of medical services for a population of over 200,000 prepaid Health Plan members. Recently renovated and expanded medical center facilities are within convenient commuting distance to virtually any bay area city and the extensive cultural and recreational activities of northern California. As part of our large, multispecialty group practice, you would enjoy an excellent salary, generous fringe benefits, a flexible schedule, and the opportunity for academic affiliation with prestigious local institutions. Send CV to Winslow Wong, MD, Attn: Administration, Kaiser Permanente Medical Center, 27400 Hesperian Blvd, Hayward, CA 94545. EOE.

NORTHERN CALIFORNIA—SAN FRANCISCO BAY AREA. Leading HMO is seeking BC/BE physician to staff a busy urban, full-service Emergency Department with the possibility of administrative advancement. Kaiser Permanente is a large pre-paid HMO offering competitive salary, job security, shareholder status, and generous benefits including health care, life insurance, disability insurance, sick leave, mortgage assistance, and educational leave. Please address all inquiries to David Witt, MD, Emergency Dept, Kaiser Permanente Medical Center, 1200 El Camino Real, South San Francisco, CA 94080-3299; or call (415) 742-2516. EOE.

INTERNIST WANTED to share practice (part-time) with same in beautiful Bellingham, Washington. Women encouraged to apply. Carletta Vanderbilt, MD, 2950 Squalicum Parkway, Bellingham, WA 98225; (206) 671-7140. Needed by April 1, 1990.

PHYSICIANS WANTED

HEALTH OFFICER

Fresno County Department of Health has an excellent opening for Health Officer/Medical Director. Responsibilities include medical consultation, liaison with medical community, media presentations, medical peer review, communicable diseases. Contract arrangement with salary and time commitment negotiable. Fresno offers outstanding lifestyles, recreation, and housing values. Please send CV to **George Bleth, Director of Health, Fresno County Dept of Health, PO Box 11867, Fresno, CA 93775; (209) 445-3200.**

KAISER PERMANENTE
Good People. Good Medicine

NORTHERN CALIFORNIA

Several positions available for Family Practice, Internal Medicine, and most medical subspecialties. We are a young, aggressive group in a well known prepaid group practice HMO organization with excellent benefits and a very reasonable call schedule. You will have a rewarding practice opportunity with ample time to enjoy the mountains and San Francisco which are nearby. If interested please call or send CV to Physician Recruitment, Administration, The Permanente Medical Group, Inc, 1305 Tommydon St, Stockton, CA 95210; (209) 476-3300.

SACRAMENTO KAISER PERMANENTE. BC/BE Family Practitioners needed to join large group of Family Practitioners providing ambulatory and inpatient care in a large prepaid health plan. Excellent working environment with strong specialty support. Outstanding financial package. Sacramento is a growing metropolitan area with good schools and recreational activities. Close to San Francisco and Lake Tahoe. If interested, please contact Stuart Hahn, MD, The Permanente Medical Group, Inc, 3240 Arden Way, Sacramento, CA 95825; or call (916) 973-5546. EOE.

SACRAMENTO AMBULATORY / URGENT CARE. Family Practitioners/Internists needed to staff adult urgent care center in Sacramento. Part-time shifts available. Clinic operates seven days per week, 12 hours per day. Excellent hourly remuneration. Benefits possible. Contact Stuart Hahn, MD, (916) 973-5546, or request application from Carolyn Whelan, Physician Recruiting, The Permanente Medical Group, Inc, 2025 Morse Ave, Sacramento, CA 95825. EOE.

EUGENE CLINIC, EUGENE, OREGON

Dynamic 55 physician multispecialty group with seven locations seeks BC/BE physicians in the following specialties: Dermatology, Family Practice, Geriatrics, Infectious Diseases, Internal Medicine, OB/GYN, Occupational Medicine, Orthopedics, General Surgery (breast disease focus), Urology. Eugene, attractive university town within 60 mile radius of Cascade Mountains and Oregon coast, offers superlative life-style, fine school system, active and varied cultural opportunities, and unlimited recreation. Qualified candidates send CV and three letters of reference to:

Physician Recruiter
1162 Willamette St
Eugene, OR 97401

PHYSICIANS WANTED

OREGON

Excellent opportunity for BC/BE General Internist with large multispecialty group in Portland metropolitan area. Group provides comprehensive medical care to 350,000 members of established northwest HMO. Position offers wide range of Internal Medicine and ample opportunity for subspecialty consultation within collegial professional environment. Competitive salary and benefit package, including generous pension program, sabbatical leave, and professional liability coverage. Forward inquiry and CV to:

Fred M. Nomura, MD
Regional Medical Director
Northwest Permanente, PC
3600 N. Interstate Ave
Portland, OR 97227

INVASIVE CARDIOLOGIST. To join a busy 25 person multispecialty group practice. The setting is in beautiful western Washington between Seattle and Vancouver, British Columbia, Canada. Competitive starting salary and benefit program. Send CV to Shane S. Spray, 1400 E. Kincaid, Mount Vernon, WA 98273.

PHYSICIAN WANTED. Full-time General Internist/Family Practitioner BC/BE, to join primary care group in San Diego area. Excellent salary, bonus, and benefits. Send CV to Douglas P. Mooney, Medical Director, 1011 Camino Del Rio S., Ste 450, San Diego, CA 92108.

LOS ANGELES COUNTY—OB/GYN. Two young, boarded OB/GYNs, practicing in Los Angeles County community of 116,000 for six years, need a third member to join their rapidly growing practice. Early partnership. Send CV to Manager, Professional Relations, Humana Inc, Dept HH-1A, 500 W. Main St, Louisville, KY 40201-1438; or call toll-free 1 (800) 626-1590.

PHYSICIANS, Arizona State University. BC/BE Primary Care Physicians in Internal Medicine, Family Practice, or Pediatrics for outpatient clinic. Duties: office-type General Medicine, Gynecology, Surgery, Orthopedics. Qualifications: graduate AMA accredited medical school, Arizona licensed/eligible, DEA registration, interest in college students within prevention and wellness education preferred. No nights or weekends. Send CV or résumé to Arizona State University, Personnel Department, Tempe, AZ 85287-1403. Inquiries to Pamela F. Tom, MD, (602) 965-5277. AA/EOE.

BC/BE GENERAL INTERNISTS, SACRAMENTO, CALIFORNIA. Established Department of Medicine within successful, stable medical group experiencing steady growth. Pleasant practice setting where physicians are free to practice the highest quality medicine with full access to diagnostic, therapeutic, and consultative services. We have affiliation with University of California, Davis, providing a substantial part of their residency programs. We offer outstanding starting salary and advancement, full benefits including excellent in-house CME and retirement package. Attractive Sacramento community with affordable cost of living. This is a quality career opportunity. Please call or send CV to Dennis Ostrem, MD, The Permanente Medical Group, 2025 Morse Ave, Sacramento, CA 95825; (916) 973-5781. EOE.

ORTHOPEDIC SURGEON AND NEUROSURGEON. BC for well established disability evaluation office in Sacramento. Full- or part-time, regular weekday hours, benefits available. Send CV to PO Box 160408, Sacramento, CA 95816.

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PHYSICIANS WANTED

PHYSICIAN ADMINISTRATOR
Southern California

CIGNA Healthplans of California—a staff model HMO committed to providing innovative, quality health care to 400,000 members in southern California—is seeking a Primary Care Physician to assume the challenging responsibilities of Physician Administrator at one of our 30 health care centers.

You will maintain an active clinical practice with a proportion of time dedicated to leadership and management of physician and support staff. Qualifications must include Board Certification in a clinical specialty and prior management experience. Excellent compensation and benefit package, including bonus plan.

Call collect or send CV in confidence to:

Robert Harrington, MD
Professional Recruitment Dept
CIGNA Healthplans of California
505 N. Brand Blvd, Ste 400-49
Glendale, CA 91203
(818) 500-6570

An Equal Opportunity Employer

EMERGENCY PHYSICIAN to join established group at attractive, well-equipped emergency room, with excellent nursing, attending staff, in San Francisco. $100K per year. Malpractice paid. Contact Rob Hemmick, MD, 450 Stanyan St, San Francisco, CA 94117; (415) 750-5700.

ACADEMIC GENERAL INTERNIST. Innovative Internal Medicine residency seeking enthusiastic teacher/clinician. Opportunity to be a member of a supportive team of faculty providing primary care training. Responsible for both inpatient and outpatient supervision. Will be involved in curriculum development and evaluation. Send CV to Mark Rosenberg, MD, Department of Medical Education, Providence Medical Center, 4805 NE Glisan St, Portland, OR 97213-2967.

VA MEDICAL CENTER, Long Beach, California is recruiting a physician. Internist, Primary Care, or other medical subspecialty needed for acute admitting ward, long term, or outpatient care in new state-of-the-art spinal cord injury center. 120 beds, 15,000 outpatient visits per year. All diagnostic modalities including MRI, Hyperbaric Oxygen, Extracorporeal Shockwave Lithotripsy, operating and neuro-urological suite. This 120-bed facility is located next to Pacific Ocean. Academic affiliation with University of California, Irvine, teaching/research encouraged. Salary and benefits are competitive for BC candidate. Contact Michael Vulpe, MD, VA Medical Center (128), 5901 E. 7th St, Long Beach, CA 90822; or call (213) 494-5701. Equal Opportunity Employer.

CALIFORNIA—NORTH SAN FRANCISCO BAY AREA. Excellent opportunity for BC/BE Family Practitioner to join our growing department in Fairfield. Multispecialty clinic emphasizing personalized care. Full hospital privileges including ICU/CCU, but no Obstetrics. Very favorable call schedule. Prepaid HMO practice provides excellent salary, benefits. Forward CV to Steven Freedman, MD, Kaiser Permanente, 1650 Gateway Blvd, Fairfield, CA 94533; (707) 427-4260. EOE.

GENERAL INTERNIST, BC/BE, needed for a position with suburban satellite clinic of a Seattle area, multispecialty group practice. Diverse patient population includes managed care, fee-for-service, retired and active military. Competitive salary and excellent benefits. Contact Mary Anderson, Pacific Medical Center, 1200 12th Ave S., Seattle, WA 98144; (206) 326-4111.

PHYSICIANS WANTED

Western States OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to:
Western States Physician Services,
5414 E. Montecito, Fresno, CA 93727.
Or call (209) 252-3047.

SPINE SURGEON, SOUTHERN CALIFORNIA

An Orthopedic Surgeon with training in Spine Surgery is needed to join two busy, well established Orthopedic Surgeons in Los Angeles County. Unlimited potential since this expertise is not represented in the group's service area. For more information about this opportunity, call toll free 1 (800) 626-1590, or send your CV to

Gordon Crawford, Professional Relations
Humana Inc, Dept HH-1B
500 W. Main St
Louisville, KY 40201-1438

CALIFORNIA CENTRAL COAST. Seeking BC/BE Family Physician to join established group of 11 BC physicians in a smog free, family oriented, growing community north of Santa Barbara. Full range of Family Practice including Obstetrics. Guaranteed competitive salary plus excellent benefits. Opportunity to become full partner after one year. Send CV or call William Diebner, Administrator, 136 N. Third St, Lompoc, CA 93436; (805) 736-1253.

FAMILY PRACTICE PHYSICIAN. Full-time in a busy walk-in medical clinic. Located in Visalia, California (Tulare County). Malpractice insurance, good salary, etc. Please call (209) 627-5555 for more information.

FAMILY PRACTITIONER BC/BE for rural health clinic at the foot of Sequoia National Park. Physician keeps all hospitalization, the clinic staff will do the billing. Send CV and salary history to Ms Elia Garcia, Woodlake Family Health Center, 180 E. Antelope, Woodlake, CA 93286; or call (209) 564-3538. EOE.

FULL-TIME TRAVEL REQUIRED (one year minimum). Health research organization needs physicians for National Health and Nutrition Examination Survey sponsored by the US Public Health Service. Individuals will be part of a large medical team conducting health examinations in government examination centers traveling to 88 areas of the US through 1993. Physicians must be licensed in one state and specialized in Internal or Family Medicine. Competitive salaries, paid malpractice, per diem, car, four weeks paid vacation per year, holidays, and health, life, dental, disability insurance offered. Call Beverly Geline at (800) 937-8281, ext 8248. Westat, Inc, Rockville, MD. EOE/M/F/V/H.

SAN DIEGO. Well established multispecialty group composed of Family Physicians, General Internists, OB/GYNs, Pediatricians, General Surgeons, ENT, and Ophthalmologist is expanding. Those interested in joining a vital private practice group, with emphasis in primary care and seeing fee-for-service and managed care patients, are welcome to send CV to Miriam Stephens Drake, 1450 Frazee Rd, Ste 605-1, San Diego, CA 92108; (619) 295-0599.

PATHOLOGY DIRECTOR, SOUTHERN CALIFORNIA—BC clinically/anatomically trained with three to five years community hospital director experience needed to run pathology dept in 230-bed community hospital. Beautiful beach location in moderate sized city with excellent outdoor activity opportunities. Send CV to Administration, Community Memorial Hospital, Loma Vista at Brent, Ventura, CA 93003; or call (805) 652-5005.

INTERNIST BC/BE to join two BC Internists in busy office and hospital practice in Salt Lake City area. Send CV to Office Manager, Alta View Internal Medicine Associates, 9720 S. 1300 E., Ste E-110, Sandy, UT 84094.

PHYSICIANS WANTED

INVASIVE CARDIOLOGISTS

Your choice of private practice opportunities:

PHOENIX, ARIZONA — Join a nationally recognized Cardiology group in their suburban satellite office. Practice experience preferred, but candidates completing fellowship will be considered.

DENVER, COLORADO — Two opportunities for the north Denver suburb of Thornton: busy, well-established two-man group of board certified Cardiologists seeking a third member; or a solo Cardiologist seeking an associate.

For further information, send your curriculum vitae to: Manager, Professional Relations, Humana Inc., Dept. HH-1, 500 West Main Street, Louisville, KY 40201-1438. Or call TOLL-FREE 1-800-626-1590.

Humana®

FACULTY POSITION. The University of California, San Francisco affiliated Family Practice residency program, located in beautiful Monterey County, is seeking full-time BC/BE Family Physician faculty member. Responsibilities to include inpatient and outpatient teaching, clinic practice, and administrative duties; previous academic experience and special interest in Gerontology desirable. Please send CV to Stephen F. Voorhies, Director, Family Practice Residency Program, Natividad Medical Center, PO Box 81611, Salinas, CA 93912-1611. AA/EOE.

PUGET SOUND. BC/BE Family Practitioner needed to join three other well established young Family Practitioners in successful half-time practice 30 minutes from Seattle. Strong Family Practice community. Excellent consultant relationships. Obstetrics optional, but preferred. Beautiful area with ample recreational and cultural opportunities. Contact Dan Goodman, MD, 1111 Pacific Ave, Everett, WA 98201; (206) 259-7255.

SAN FRANCISCO PENINSULA (SAN MATEO). Two Internists seeking associate for General Internal Medicine practice in San Mateo on San Francisco peninsula. A 250-bed hospital one block from office. Weekly continuing medical education program in the hospital by Stanford professors. Ideal weather. Mountains and ocean nearby. Excellent call rotation. 18 miles from Stanford and University of California medical schools. Guaranteed income. Send résumé to Stephen Marks, MD, 109 St. Matthews Ave, San Mateo, CA 94401; (415) 343-2737.

UNIVERSITY HEALTH SERVICE PHYSICIAN. Washington State University. Join eight other Primary Care Physicians serving 16,000 students. Nine-month academic year position plus negotiable summer work for additional compensation. Medical teaching appointment possibility. MD or DO degree and Washington license required. BE/BC Family Practice or Primary Care Physician with practice experience preferred. CV and names, addresses, and telephone numbers of three references to Richard L. Fredericks, MD, Chair, Search Committee, Student Health Service, Washington State University, Pullman, WA 99164-2302; (509) 335-3575. Applications will be accepted until the position is filled. Washington State is an EO/AA educator and employer. Protected group members are encouraged to apply.

FAMILY PRACTICE, INTERNAL MEDICINE, AND OB/GYN. Immediate opportunities in midwest and southeastern states. Competitive income and benefit packages. Contact Darell McWilliams, Mediline, 210 25th Ave N, Nashville, TN 37203; (615) 327-1910.

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PHYSICIANS WANTED

MEDICAL EXAMINER

Shasta County, California is seeking to fill the position of Medical Examiner. Approximately 150 autopsies per year performed and there is a staff of five people. It requires possession of a valid California Physicians and Surgeons Certificate and BC in Pathology at the time of appointment.

Redding, the county seat, is a city of 60,000 people located adjacent to the Cascade Mountains in northern California in a semi-rural area. It has outstanding living conditions and a relatively low cost of living.

Contact:
Shasta County Personnel Dept
1500 Court St
Courthouse, Room 105
Redding, CA 96001
Telephone (916) 225-5515

EXCELLENT INTERNAL MEDICINE OPPORTUNITY in California. Two energetic BC physicians seek conscientious associate with interest in critical care and geriatrics to join stellar practice in family oriented community. Superb location for year-round recreation—downhill skiing, boating, and hiking in nearby Sequoia National Park. Competitive financial package leading to partnership includes paid malpractice, disability and health insurance, relocation and interviewing expenses. Contact Paul Byerlein, Jackson and Coker, 115 Perimeter Center Pl, Ste 380 WJM9, Atlanta, GA 30346; 1 (800) 544-1987 or 1 (800) 888-5530.

ASSISTANT PROFESSOR level full-time position available in the Department of Pathology, University of California, San Francisco. Subspecialties: OB/GYN Pathology and/or Cytopathology with service duties in the dysplasia/colposcopy clinic. Expertise in immunocytochemistry and/or computer science and/or diagnosis/treatment of cervical neoplasia (FNA biopsy and sexually transmitted disease interests also desirable). Teaching: medical students, housestaff, interdepartmental conferences. Research areas: human papillomavirus, immunopathology, cell biology. Requirements: California medical license or eligibility, BC/BE. Send CV to Department of Pathology Search Committee, University of California, San Francisco, San Francisco, CA 94143-0506. The University of California is an Equal Opportunity/Affirmative Action Employer. Women and minorities are encouraged to apply.

GENERAL INTERNIST. Steinbeck country, BC/BE General Internist to join dynamic group; includes hospital care, shared call. Spanish helpful. Many visiting consultants, good guarantee with chance for early partnership. Many fringes. One hour to Monterey, three hours to San Francisco. Call or write Helen Poole, 210 Canal St, King City, CA 93930; (408) 385-5471.

BC/BE FAMILY PRACTITIONER needed for small city in central California. Position offers very competitive salary and benefit package. Full Family Practice including routine OB. Malpractice paid. Area offers excellent family life-style amenities, recreation and easy access to major cities. Interested candidates please send CV to Number 185, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

YELLOWSTONE NATIONAL PARK. Physician to cover outpatient clinic, emergency room, and inpatient at Lake Hospital from Memorial Day to mid September 1990. Send CV to Yellowstone Park Medical Services, 707 Sheridan Ave, Cody, WY 82414 or call (307) 578-2461.

PHYSICIANS WANTED

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Three residency-trained BC Family Practitioners seek a fourth who is a BE/BC to join them immediately in their community health center practice. Located on the eastern slopes of the Sierras in northeastern California. Practice entails a full scope of Family Practice including Obstetrics. Full hospital privileges. Excellent opportunity for recreation in local mountains including fishing, hiking, bicycling, camping, waterskiing, windsurfing, sailing, and in the winter both downhill and cross-country skiing. Includes a complete benefit package: malpractice coverage, health insurance, vacation, CME, etc. Salary commensurate with experience. Staff includes two family nurse practitioners, one physician assistant, family therapist, registered dietician, two health educators, and two prenatal instructors. Teaching opportunities available. If interested, send CV to **NRHC, Inc, 1306 Riverside Dr, Susanville, CA 96130, Attn: Paul W. Holmes, MD, Medical Director; or call (916) 257-5563.**

PRO MEDICAL DIRECTOR. Statewide California Medical Review Organization is seeking a physician with substantial clinical, management, and review experience. Responsibilities include assessing the quality/utilization of medical care. The overall supervision of physician advisors and day to day monitoring of medical decisions. Requirements: (1) minimum five years clinical practice; (2) minimum two years management experience or equivalent; (3) board certification; (4) California license. Position located in Bakersfield, California. Send CV and references with salary requirements to CMRI, 60 Spear St, #500, San Francisco, CA 94105. Attn: Joyce, Employment Rep. An affirmative action employer.

INVASIVE CARDIOLOGIST BC/BE Cardiologist to join four busy Invasive Cardiologists in Pacific Northwest. Extensive training in PTCA required. Practice heavily oriented towards consultative cardiology and acute care. Reply to Number 186, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

SOUTHERN CALIFORNIA (San Diego County) thriving coastal city of Encinitas. Three physician Family Practice group plus Psychologist seeking residency trained Family Practitioner. Located in new primary care/multispecialty full service facility eight minutes from hospital. Send CV to NCFMG, 477 El Camino Real, A306, Encinitas, CA 92024.

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OUTSTANDING SOUTHWEST OPPORTUNITY

BC Family Practice Physician seeking second or third physician Family Practitioner (or Internist) in one of the fastest growing areas of US. The practice is situated in a new medical office building on the campus of modern, progressive Northwest Hospital in suburban northwest Tucson.

Substantial fee-for-service opportunity in this beautiful southwestern community 40 minutes from skiing, four and one-half hours from Mexico beaches. Excellent call coverage schedule and financial package. Contact **Physician Recruiter, Northwest Hospital Administration, 6200 N. La Cholla Blvd, Tucson, AZ 85741; (602) 742-9000, ext. 100.**

PHYSICIANS WANTED

UNIQUE CLINICAL INTERNAL MEDICINE FELLOWSHIP. UCLA Department of Medicine offering fourth year training in Internal Medicine, through the Kennamer Fellowship, supported by the Albert Parvin Foundation. Fellowship begins July 1, 1991 for candidates BC/BE in Internal Medicine. A one year fellowship for practice careers. One fellow will be based at each of UCLA's major affiliates: Cedars-Sinai, Harbor, UCLA-San Fernando Valley, UCLA and Wadsworth/VA. Stipend $28,500 plus health insurance and worker's compensation. For forms and details write Roy T. Young, MD, UCLA Dept of Medicine, 32-115 CHS, 10833 Le Conte Blvd, Los Angeles, CA 90024. Applications deadline March 30, 1990. Interviews by invitation. All applicants notified before July 1, 1990. Equal opportunity/affirmative action employer.

PRACTICES AVAILABLE

BEAUTIFUL NAPA VALLEY, CALIFORNIA. Solo Psychiatric practice. Good clientele. Potential for growth as desired. Physician retiring. Residence available. Call David Lucchesi, (707) 552-3831.

WELL ESTABLISHED GENERAL INTERNIST'S PRACTICE. Excellent coverage and income. Silicon Valley. Physician will retire incrementally. U.S. trained BE/BC only, please. Reply to Number 178, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

ORTHOPEDIC PRACTICE AVAILABLE. Excellent opportunity to take over successful, well established practice. 40,000 population regional medical center in Idaho with drawing area of 200,000. State-of-the-art hospital and surgical center. Solo practice, well equipped, well staffed office in new 25 doctor multispecialty center. Excellent referral base. Easy living in beautiful four season country. Negotiable terms. Reply to Number 180, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

CALIFORNIA. Sunny, warm southern California resort town, Palm Springs area. Long established. Practice suitable for Internal Medicine or Family Practice. Two hospitals. Reason: retiring. Great potential and golf! Reply to Number 181, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PRACTICE FOR SALE. Internist wanted for established solo practice. Coverage evenings and weekends available. Office adjacent to modern 180-bed acute care hospital. Medical service area 80,000. Please reply to Herbert Waechtler, MD, 980 Trancas, Ste 5, Napa, CA 94558; (707) 224-6556.

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INTERNAL MEDICINE OR FAMILY PRACTICE. Solo Internist retiring, office adjacent to one of two hospitals in mid-Puget Sound, city of 65,000 in Washington. Rapidly expanding area. Free parking, equipment, records, and experienced personnel available. (206) 252-1088.

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(Continued on Page 105)

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FAMILY PRACTICE. Retiring after 37 years in same prime San Francisco location. Practice emphasizes treatment of pain by acupuncture. Will train. For information call Harry W. Tong, Agent, (415) 363-0101.

FOR SALE. Established, busy Urology practice in southwestern New Mexico. No investment required. Excellent year 'round climate and outdoor recreational opportunities. Call collect, Pierson Deming, MD, (505) 388-1561 (office) or (505) 388-4557 (home); or call Steve Jacobson, Administrator, Gila Regional Medical Center, (505) 388-1591.

INTERNAL MEDICINE PRACTICE FOR SALE in Grants, New Mexico. Grossing $220K, low overhead. Includes part ownership in medical building. Excellent opportunity with practice growth 20 percent in 1989. Close to major city, skiing, great for outdoor activity. Financial support available. Call R. Avedisian, (505) 287-8889.

PSYCHIATRY PRIVATE PRACTICE. San Diego desirable area, transferrable patient base and referral sources. Considerable capacity for growth. Gross averages $120,000 on half-time. Contact Practice Consultants, (619) 528-2321, Dr Bernard Press, Broker.

NORTHERN AND CENTRAL CALIFORNIA. Established practices available: Dermatology, Family, Internal Medicine, OB/GYN, Ophthalmology, Pediatrics, Plastic Surgery, and Urology. Reasonable terms and prices. Call/write Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (415) 376-0762, FAX (415) 376-0813.

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MEETINGS

41st ANNUAL MEETING—SPOKANE SOCIETY OF INTERNAL MEDICINE
March 9, 10, 1990. "Advances in Clinical Cardiology." National faculty, nine hours CME, Ridpath Hotel, Spokane, Washington. Cost: Physician/Nonmember—$75; Physician/Member—$50; Associated Professionals—$50; Residents—$10. Contact **Linda Browne, PO Box 8443, Spokane, WA 99203; (509) 448-2513.**

FAMILY PRACTICE DAY
MARCH 8, 1990
7:30 A.M. - 5:00 P.M.
SWEDISH HOSPITAL MEDICAL CENTER
GLASER AUDITORIUM
(206) 386-2265

EXAMINATIONS

The American Board of Quality Assurance and Utilization Review Physicians Certification Examination and Lecture Sites for 1990:

Feb. 23-25	Phoenix, AZ
May 25-27	Chicago, IL
Sept. 21-23	San Francisco, CA

For further information contact:
ABQAURP
Murdock Professional Center, 1777 Tamiami Trail, Box 12 WJM1, Port Charlotte, FL 33948. Ph.#813-743-2425.

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SYMPOSIUMS

ADVANCES IN INTERNAL MEDICINE
Postgraduate Symposium
March 5-9, 1990
Snowbird, Utah

Program Chairman: M. Berenson, M.D.
Physician's Fee: $300
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Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympathicolytic and mydriatric. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:
1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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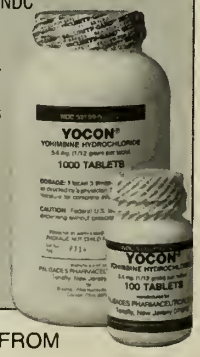

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Alaska State Medical Association—2401 E 42nd Ave, Suite 104, Anchorage 99508. (907) 562-2662. Annual Meeting: 1990, date and location to be announced.

Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 7-9, 1990, Wyndham, Paradise Valley.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 2-7, 1990, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: 1990, date and location to be announced.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: 1990, date and location to be announed.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 26-28, 1990, Sun Valley.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: 1990, date and location to be announced.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: June 21-23, 1990, Hyatt, Lake Tahoe.

New Mexico Medical Society—7770 Jefferson, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: May 4-5, 1990, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): 1990, date and location to be announced.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: 1990, date and location to be announced.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: 1990, date and location to be announced.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 14-16, 1990, Jackson Lake Lodge, Moran.

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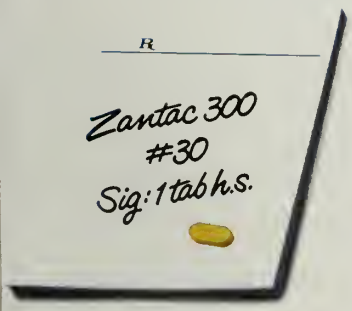

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ZANTAC® 300 Tablets
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in ZANTAC® product labeling.

INDICATIONS AND USAGE: ZANTAC® is indicated in:
1. Short-term treatment of **active duodenal ulcer**. Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer**. Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD)**. Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: General: 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.
2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION**). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions which suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, E coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with oral ZANTAC®. The relationship to ZANTAC therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ZANTAC administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: Rare reports of tachycardia, bradycardia, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid IV for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Reversible blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. Rare cases of agranulocytosis or of pancytopenia, sometimes with marrow hypoplasia, have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ZANTAC® (ranitidine hydrochloride) and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg twice daily. An alternate dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ZANTAC® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day.

GERD: The current recommended adult oral dosage is 150 mg twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: ZANTAC® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) and unit dose packs of 100 tablets (NDC 0173-0393-47).

ZANTAC® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 tablets (NDC 0173-0344-42) and unit dose packs of 100 tablets (NDC 0173-0344-47).

Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

August 1987

Glaxo

Glaxo Inc.
Research Triangle Park, NC 27709

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October 1987

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VASOTEC is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

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VASOTEC is available in 2.5-mg, 5-mg, 10-mg, and 20-mg tablet strengths.

Contraindications: VASOTEC® (Enalapril Maleate, MSD) is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor

Warnings: *Angioedema* Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including VASOTEC In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms Angioedema associated with laryngeal edema may be fatal **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered.** (See ADVERSE REACTIONS.)

Hypotension: Excessive hypotension is rare in uncomplicated hypertensive patients treated with VASOTEC alone Patients with heart failure given VASOTEC commonly have some reduction in blood pressure, especially with the first dose, but discontinuation of therapy for continuing symptomatic hypotension usually is not necessary when dosing instructions are followed, caution should be observed when initiating therapy (See DOSAGE AND ADMINISTRATION.) Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death, include those with the following conditions or characteristics heart failure, hyponatremia, high-dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology It may be advisable to eliminate the diuretic (except in patients with heart failure), reduce the diuretic dose, or increase salt intake cautiously before initiating therapy with VASOTEC in patients at risk for excessive hypotension who are able to tolerate such adjustments (See PRECAUTIONS, *Drug Interactions* and ADVERSE REACTIONS.) In patients at risk for excessive hypotension, therapy should be started under very close medical supervision and such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased Similar considerations may apply to patients with ischemic heart disease or cardiovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline A transient hypotensive response is not a contraindication to further doses of VASOTEC, which usually can be given without difficulty once the blood pressure has stabilized If symptomatic hypotension develops, a dose reduction or discontinuation of VASOTEC or concomitant diuretic may be necessary

Neutropenia/Agranulocytosis Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered

Precautions: *General Impaired Renal Function* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy In such patients, renal function should be monitored during the first few weeks of therapy

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic This is more likely to occur in patients with preexisting renal impairment Dosage reduction and/or discontinuation of the diuretic and/or VASOTEC may be required

Evaluation of patients with hypertension or heart failure should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hyperkalemia Elevated serum potassium (>5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy Hyperkalemia was a cause of discontinuation of therapy in 0 28% of hypertensive patients. In clinical trials in heart failure, hyperkalemia was observed in 3 8% of patients, but was not a cause for discontinuation

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with VASOTEC (See *Drug Interactions*.)

Surgery/Anesthesia In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients.

Angioedema Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician

Hypotension Patients should be cautioned to report lightheadedness, especially during the first few days of therapy It actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure, patients should be advised to consult with the physician

Hyperkalemia Patients should be told not to use salt substitutes containing potassium without consulting their physician

Neutropenia Patients should be told to report promptly any indication of infection (e g , sore throat, fever) which may be a sign of neutropenia

NOTE As with many other drugs, certain advice to patients being treated with enalapril is warranted This information is intended to aid in the safe and effective use of this medication It is not a disclosure of all possible adverse or intended effects

Drug Interactions

Hypotension. Patients on Diuretic Therapy. Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Agents Causing Renin Release The antihypertensive effect of VASOTEC is augmented by antihypertensive agents that cause renin release (e g , diuretics).

Other Cardiovascular Agents. VASOTEC has been used concomitantly with beta-adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine prazosin, and digoxin without evidence of clinically significant adverse interactions

Agents Increasing Serum Potassium VASOTEC attenuates potassium loss caused by thiazide-type diuretics Potassium-sparing diuretics (e g , spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium Potassium-sparing agents should generally not be used in patients with heart failure receiving VASOTEC

Lithium: Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant VASOTEC and lithium and were reversible upon discontinuation of both drugs It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium

Pregnancy – Category C There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril but did not occur when these animals were supplemented with saline Enalapril was not teratogenic in rabbits However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose)

Radioactivity was found to cross the placenta following administration of labeled enalapril to pregnant hamsters

There are no adequate and well-controlled studies of enalapril in pregnant women However, data are available that show enalapril crosses the human placenta Because the risk of fetal toxicity with the use of ACE inhibitors has not been clearly defined, VASOTEC® (Enalapril Maleate MSD) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Postmarketing experience with all ACE inhibitors thus far suggests the following with regard to pregnancy outcome Inadvertent exposure limited to the first trimester of pregnancy has not been reported to affect fetal outcome adversely Fetal exposure during the second and third trimesters of pregnancy has been associated with fetal and neonatal morbidity and mortality

When ACE inhibitors are used during the later stages of pregnancy, there have been reports of hypotension and decreased renal perfusion in the newborn Oligohydramnios in the mother has also been reported, presumably representing decreased renal function in the fetus Infants exposed *in utero* to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion with the administration of fluids and pressors as appropriate Problems associated with prematurity such as patent ductus arteriosus have occurred in association with maternal use of ACE inhibitors, but it is not clear whether they are related to ACE inhibition, maternal hypertension, or the underlying prematurity

Nursing Mothers Milk in lactating rats contains radioactivity following administration of ^{14}C enalapril maleate It is not known whether this drug is secreted in human milk Because many drugs are secreted in human milk caution should be exercised when VASOTEC is given to a nursing mother

Pediatric Use Safety and effectiveness in children have not been established

Adverse Reactions: VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2987 patients.

HYPERTENSION The most frequent clinical adverse experiences in controlled trials were headache (5 2%), dizziness (4 3%), and fatigue (3%)

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were diarrhea (1 4%), nausea (1 4%), rash (1 4%), cough (1 3%), orthostatic effects (1 2%), and asthenia (1 1%).

HEART FAILURE The most frequent clinical adverse experiences in both controlled and uncontrolled trials were dizziness (7 9%), hypotension (6 7%), orthostatic effects (2 2%), syncope (2 2%), cough (2 2%), chest pain (2 1%), and diarrhea (2 1%)

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in both controlled and uncontrolled clinical trials were fatigue (1 8%), headache (1 8%), abdominal pain (1 6%), asthenia (1 6%) orthostatic hypotension (1 6%), vertigo (1 6%), angina pectoris (1 5%), nausea (1 3%), vomiting (1 3%), bronchitis (1 3%) dyspnea (1 3%), urinary tract infection (1 3%), rash (1 3%), and myocardial infarction (1 2%)

Other serious clinical adverse experiences occurring since the drug was marketed or adverse experiences occurring in 0 5% to 1% of patients with hypertension or heart failure in clinical trials in order of decreasing severity within each category

Cardiovascular Cardiac arrest, myocardial infarction or cerebrovascular accident possibly secondary to excessive hypotension in high-risk patients (see WARNINGS, *Hypotension*); cardiac arrest, pulmonary embolism and infarction, rhythm disturbances, atrial fibrillation, palpitation

Digestive Ileus, pancreatitis, hepatitis or cholestatic jaundice, melena, anorexia, dyspepsia, constipation, glossitis, stomatitis

Musculoskeletal Muscle cramps

Nervous/Psychiatric Depression, confusion, ataxia, somnolence, insomnia, nervousness, paresthesia

Urogenital Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION)

Respiratory Bronchospasm, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection

Skin Herpes zoster, urticaria, pruritus, alopecia, flushing hyperhidrosis

Special Senses Blurred vision, taste alteration, tinnitus.

A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgias/arthritis, myalgias, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash, and other dermatologic manifestations

Angioedema Angioedema has been reported in patients receiving VASOTEC (0 2%) Angioedema associated with laryngeal edema may be fatal If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately (See WARNINGS.)

Hypotension In the hypertensive patients, hypotension occurred in 0 9% and syncope occurred in 0 5% of patients following the initial dose or during extended therapy Hypotension or syncope was a cause for discontinuation of therapy in 0 1% of hypertensive patients. In heart failure patients, hypotension occurred in 6 7% and syncope occurred in 2 2% of patients Hypotension or syncope was a cause for discontinuation of therapy in 1 9% of patients with heart failure (See WARNINGS.)

Clinical Laboratory Test Findings

Serum Electrolytes Hyperkalemia (see PRECAUTIONS), hyponatremia

Creatinine, Blood Urea Nitrogen In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0 2% of patients with essential hypertension treated with VASOTEC alone Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis (See PRECAUTIONS.) In patients with heart failure who were also receiving diuretics with or without digitalis, increases in blood urea nitrogen or serum creatinine, usually reversible upon discontinuation of VASOTEC and/or other concomitant diuretic therapy, were observed in about 11% of patients Increases in blood urea nitrogen or creatinine were a cause for discontinuation in 1 2% of patients.

Hemoglobin and Hematocrit Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0 3 g% and 1 0 vol %, respectively) occur frequently in either hypertension or heart failure patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists In clinical trials, less than 0 1% of patients discontinued therapy due to anemia

Other (Causal Relationship Unknown) In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported A few cases of hemolysis have been reported in patients with G6PD deficiency

Liver Function Tests Elevations of liver enzymes and/or serum bilirubin have occurred

Dosage and Administration: *Hypertension* In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC The diuretic should, if possible, be discontinued for two to three days before beginning therapy with VASOTEC to reduce the likelihood of hypotension (See WARNINGS.) If the patient's blood pressure is not controlled with VASOTEC alone, diuretic therapy may be resumed.

If the diuretic cannot be discontinued, an initial dose of 2 5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour (See WARNINGS and PRECAUTIONS, *Drug Interactions*.)

The recommended initial dose in patients not on diuretics is 5 mg once a day Dosage should be adjusted according to blood pressure response The usual dosage range is 10 to 40 mg per day administered in a single dose or in two divided doses In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval In such patients, an increase in dosage or twice-daily administration should be considered If blood pressure is not controlled with VASOTEC alone, a diuretic may be added

Concomitant administration of VASOTEC with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS)

Dosage Adjustment in Hypertensive Patients with Renal Impairment. The usual dose of enalapril is recommended for patients with a creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL) For patients with creatinine clearance ≤ 30 mL/min (serum creatinine ≥ 3 mg/dL), the first dose is 2 5 mg once daily The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily

Heart Failure VASOTEC is indicated as adjunctive therapy with diuretics and digitalis The recommended starting dose is 2 5 mg once or twice daily After the initial dose of VASOTEC, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, *Drug Interactions*.) If possible, the dose of the diuretic should be reduced, which may diminish the likelihood of hypotension The appearance of hypotension after the initial dose of VASOTEC does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension. The usual therapeutic dosing range for the treatment of heart failure is 5 to 20 mg daily given in two divided doses The maximum daily dose is 40 mg Once-daily dosing has been effective in a controlled study, but nearly all patients in this study were given 40 mg. The maximum recommended daily dose, and there has been much more experience with twice-daily dosing In addition, in a placebo-controlled study which demonstrated reduced mortality in patients with severe heart failure (NYHA Class IV), patients were treated with 2 5 to 40 mg per day of VASOTEC, almost always administered in two divided doses (See CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects*.) Dosage may be adjusted depending upon clinical or hemodynamic response (See WARNINGS.)

Dosage Adjustment in Patients with Heart Failure and Renal Impairment or Hyponatremia In patients with heart failure who have hyponatremia (serum sodium < 130 mEq/L) or with serum creatinine >1 6 mg/dL, therapy should be initiated at 2 5 mg daily under close medical supervision (See DOSAGE AND ADMINISTRATION, *Heart Failure*, WARNINGS, and PRECAUTIONS, *Drug Interactions*.) The dose may be increased to 2.5 mg b i d , then 5 mg b i d and higher as needed, usually at intervals of four days or more, if at the time of dosage adjustment there is not excessive hypotension or significant deterioration of renal function The maximum daily dose is 40 mg

For more detailed information, consult your MSD Representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486 J9VS54R(818)

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YOCON®
YOHIMBINE HCl

Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympathicolytic and mydriatric. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

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References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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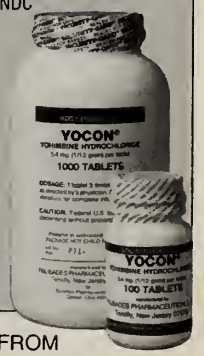

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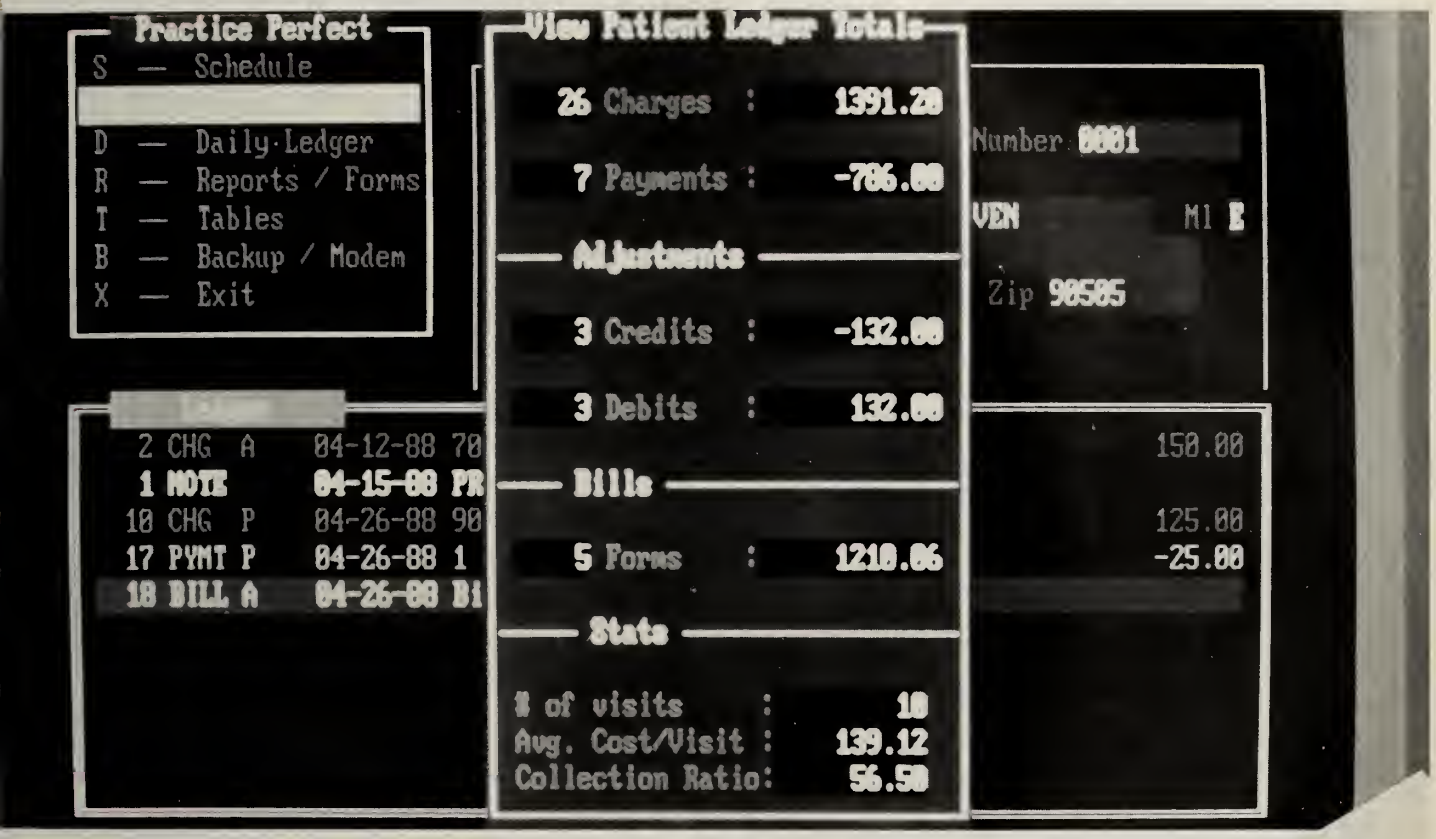

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$$\frac{240}{<35}$$

What's a common denominator of most heart attack victims?

HDL

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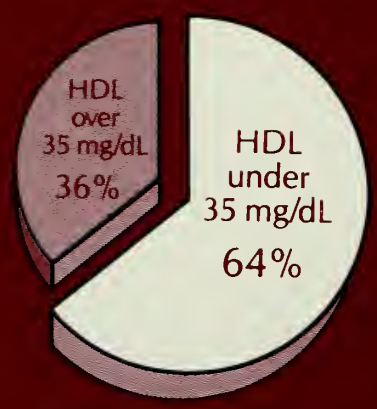
mg/dL

Mixed hyperlipidemias—elevated cholesterol *and* triglycerides—are common among heart attack victims,[1] and nearly two-thirds of people who developed myocardial infarction in the PROCAM Trial had a low (<35 mg/dL) baseline level of HDL cholesterol.[2]

HEART ATTACK PATIENTS
(PROCAM TRIAL)[2]



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—in patients whose baseline HDL was below 35 mg/dL in the landmark Helsinki Heart Study (HHS).[3]

Reduced heart attack incidence* up to 62%

—in these HHS patients and 45% in HHS patients whose baseline HDL was below the median (46.4 mg/dL). Incidence of serious coronary events was similar for LOPID and placebo subgroups with baseline HDL above the median (46.4 mg/dL).[3]

Raised HDL levels 1½ to 3 times more effectively than lovastatin

—in a 12-week, double-blind, randomized trial among patients with moderate to severe hyperlipidemia. Lovastatin achieved greater reductions in total serum cholesterol than gemfibrozil in this study population.[4]

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DRAMATICALLY REDUCES HEART ATTACK

LOPID is indicated for reducing the risk of coronary heart disease (CHD) in Type IIb patients with low HDL, in addition to elevated LDL and triglycerides, and who have had an inadequate response to weight loss, diet, exercise, and other pharmacologic agents such as bile acid sequestrants and nicotinic acid.

*Defined as a combination of definite coronary death and/or definite myocardial infarction.

References: 1. Goldstein JL, Hazzard WR, Schrott HG, Bierman EL, Motulsky AG. Hyperlipidemia in coronary heart disease. I. Lipid levels in 500 survivors of myocardial infarction. *J Clin Invest.* 1973;52:1533-1543. **2.** Assmann G, Schulte H. *PROCAM-Trial: Prospective Cardiovascular Münster Trial.* Zürich: Panscientia Verlag; 1986:8-9. **3.** Data on file, Medical Affairs Dept, Parke-Davis **4.** Tikkanen MJ, Helve E, Jäättelä A, et al. Comparison between lovastatin and gemfibrozil in the treatment of primary hypercholesterolemia: the Finnish Multicenter Study. *Am J Cardiol.* 1988;62:35J-43J.

Please see last page of this advertisement for warnings, contraindications, and brief summary of prescribing information.

Lopid® (Gemfibrozil Capsules and Tablets)

Before prescribing, please see full prescribing information.
A Brief Summary follows.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease (See WARNINGS).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

During the Helsinki Heart Study and in the 1½ year follow-up period since the trial was completed, mortality from any cause was 59 (2.9%) in the Lopid group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the Lopid group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statistically-significantly different from the 29% excess mortality seen in the clofibrate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58% greater trend in the Lopid group (43 vs 27 patients in the placebo group, p=0.056).

In the Helsinki Heart Study, the incidence of total malignancies discovered during the trial and in the 1½ years since the trial was completed was 39 in the Lopid group and 29 in the placebo group (difference not statistically significant). This includes 5 basal cell carcinomas in the Lopid group and none in the placebo group (p=0.06; historical data predicted an expected 4.7 cases in the placebo group). GI malignancies and deaths from malignancies were not statistically different between Lopid and placebo subgroups. Follow-up of the Helsinki Heart Study participants will provide further information on cause-specific mortality and cancer morbidity.

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants – Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts – Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS. 1. **Initial Therapy** – Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy** – Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions** – (A) **Lovastatin:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility** – Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p=0.1). In high dose female rats, there was a significant increase in the combined incidence of benign, and malignant liver neoplasms. In male and female mice, there were no statistically significant differences

Lopid® (Gemfibrozil Capsules and Tablets)

from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately three or ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category B** – Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to Lopid. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lopid is tumorigenic in male and female rats, the use of Lopid in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers** – Because of the potential for tumorigenicity shown for gemfibrozil in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes** – Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. **Liver Function** – Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Use in Children** – Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In the double-blind controlled phase of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group (placebo incidence in parentheses): gastrointestinal reactions, 34.2% (23.8%), dyspepsia, 19.6% (11.9%); abdominal pain, 9.8% (5.6%); acute appendicitis (histologically confirmed in most cases where data are available), 1.2% (0.6%); atrial fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant difference between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5%); fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%).

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study.

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of **musculoskeletal symptoms** (See WARNINGS), and to **abnormal liver function tests** and **hematologic changes** (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patients.

Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *Integumentary:* alopecia.

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

MANAGEMENT OF OVERDOSE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

References: 1. Frick MH, Elo O, Haapa K, et al: Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med* 1987;317:1237-1245. 2. Manninen V, Elo O, Frick MH, et al: Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA* 1988; 260:641-651. 3. Nikkila EA: Familial lipoprotein lipase deficiency and related disorders of chylomicron metabolism. In Stanbury J. B. et al. (eds.): *The Metabolic Basis of Inherited Disease*, 5th ed., McGraw-Hill, 1983, Chap. 30, pp. 622-642.

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INFORMATION FOR AUTHORS

Submitting Manuscripts

Manuscripts for consideration should be sent to the editor, Malcolm S. M. Watts, MD, PO Box 7602, San Francisco, California 94120-7602. The transmittal letter should designate one person as correspondent and include complete address, with ZIP code and telephone number.

In view of *The Copyright Revision Act of 1976*, transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns, or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* authors.

Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format and to give close attention to syntax, grammar, and spelling.

Clinical Investigation Section

Articles that authors wish to have considered for the Clinical Investigation section should be so designated in the transmittal letter. The type of articles appropriate for this section are those that describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease. An article describing a single case report will not normally be considered appropriate for this section.

Preparing Manuscripts

The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed *double-spaced throughout* (including legends, tables, and references) on one side of the paper, with 1½-inch margins. Articles should not exceed 3,000 words (less than 15 text pages typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page. Manuscripts produced with a dot-matrix printer are ordinarily not acceptable.

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Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

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Temperatures. Temperature readings should be given first in Celsius, followed by the Fahrenheit equivalent in parentheses.

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Titles are best when brief and concise. The title page should include the full name of the author(s), with degrees, academic or professional titles, complete addresses, and any institutional or other affiliations. The complete name and address of the person who will handle reprint requests also should appear on this page.

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Tables and Figures

Tables

Each table should be typed on a separate sheet of paper, be numbered consecutively in Arabic numerals, have a brief descriptive title, and have its position indicated in the text.

Illustrations (Figures)

Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and the position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

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All legends for figures should be typed together on a separate sheet of paper. Magnification and stain for photomicrographs should be indicated in parentheses.

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Journal Articles

Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, use of inclusive page numbers, and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Anderson HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978; 7:76-79

Books

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs, or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, Mass, Publishing Sciences Group, 1977 *(corporate author)*

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Any article accepted for publication should include the name of the journal (appropriately abbreviated) in which it will appear and the phrase "in press" or "accepted for publication" in place of the date of publication.

Personal Communications and Unpublished Data

This information should *not* be included in the reference list but should be given in parentheses in the body of the text. Date of communication, whether it was oral or written, and the person's name, highest academic degree, and professional affiliation should be provided.

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It is the policy of the *WJM* not to print acknowledgments, the feeling being that if a person has contributed enough to a paper to be mentioned, he or she should be included among the authors, or the contribution should be mentioned in the body of the paper or in a footnote.

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Brief manuscripts commenting on articles that have appeared in the journal, containing information of interest to physicians, or discussing issues of the day will be considered for publication. Very short reports of cases, clinical experience, clinical studies, adverse effects, and the like also will be considered. Items for the Correspondence section should not exceed 600 words and should have no more than five bibliographic references and one figure or table.

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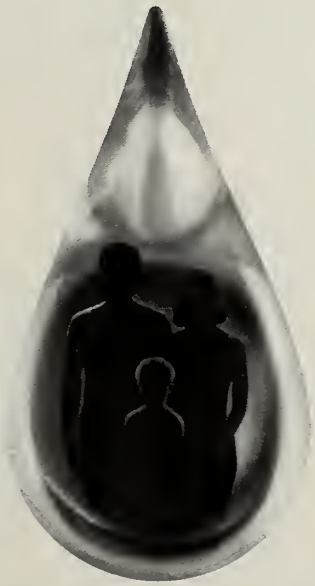

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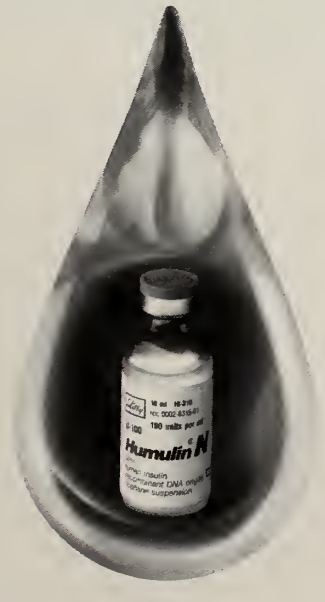

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

February 15-17—**16th Annual Frontiers in Ophthalmology.** St Luke's Medical Center and Prentice Eye Institute at Red Lion's La Posada Resort, Scottsdale. Thurs-Sat. Contact: Christine Campbell, (602) 820-7027.

February 15-17—**Emergency Care Update.** Arizona Health Sciences Center, Tucson. Thurs-Sat. Contact: (602) 626-7832.

February 16-17—**Geriatrics in a Changing Society: Enhancing Function—2nd Annual Regional, Multidisciplinary Conference.** Samaritan Institute of Gerontology, Phoenix. Fri-Sat. Contact: Jean Kiernat, (602) 239-5884.

February 22-24—**Geriatric Medicine Update and Board Certification Review Conference.** University of Arizona College of Medicine at Doubletree Hotel, Tucson. Thurs-Sat. Contact: Gail Kershner Riggs, (602) 626-6854.

February 23-24—**Mayo Clinic Update on Plastic and Reconstructive Surgery.** Marriott's Mountain Shadows Resort, Scottsdale. Fri-Sat. Contact: Mayo Clinic-Scottsdale.

February 23-25—**Anesthesia for the 1990s.** Arizona Society of Anesthesiologists, Wyndham Paradise Valley Resort, Scottsdale. Fri-Sun. Contact: Beverly Reichter, (602) 246-8901.

February 24—**Diabetes 1990: A Practical Approach to Management IV.** Good Samaritan Regional Medical Center, Phoenix Children's Hospital, and American Diabetes Association at Wyndham Paradise Valley Resort. Sat. Contact: Teri Quesnell, (602) 239-5994.

February 26-March 1—**Practical Radiology—6th Annual Course.** University of Arizona College of Medicine at Lowe's Ventana Canyon Resort, Tucson. Mon-Thurs. Contact: (602) 626-7832.

February 27-March 2—**Pediatric Update.** Phoenix Children's Hospital. Tues-Fri. Contact: Susan Fraley, (602) 239-5783.

February 28-March 2—**13th Annual Mid-Winter Symposium in OB/GYN.** Phoenix OB/GYN Society and the Department of OB/GYN, Maricopa Medical Center at Scottsdale Hilton Hotel, Scottsdale. Wed-Fri. Contact: Phoenix OB/GYN Society, (602) 266-6321.

March 1-2—**Southern Arizona Trauma Conference.** University of Arizona College of Medicine at Doubletree Hotel, Tucson. Thurs-Fri. Contact: Lorraine Haertel, PhD, (602) 626-6233.

March 1-3—**Rheumatology for the 90s: A Look Into the Future.** Westin La Paloma Resort, Tucson. Thurs-Sat. Contact: CME, Arizona Health Sciences Center, (602) 626-7832.

March 1-4—**A Continuance of Excellence.** Arizona Academy of Family Physicians, The Registry Resort, Scottsdale. Thurs-Sun. Contact: Nancy Reeves, (602) 249-2021.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Jodi Lee Smith, Postgraduate Courses, Mayo Clinic Scottsdale, (602) 391-8300.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

March 3-7—**Fourth Annual Magnetic Resonance Imaging Conference.** Barrow Neurological Institute of St Joseph's Hospital and Medical Center at Marriott's Camelback Inn Resort, Scottsdale. Sat-Wed. Contact: Kevin King, RT, (602) 285-3956.

March 8-10—**Recent Advances in Neurology and Neurosurgery—17th Annual Symposium.** Barrow Neurological Institute at Camelback Inn Resort, Scottsdale. Thurs-Sat. Contact: Toby Jardine, (602) 285-3178.

March 14—**Dean's Education Rounds.** Arizona Health Sciences Center, Tucson. Wed. Contact: Jack Roberts, (602) 626-4555.

March 23-24—**Ophthalmic Reviews.** Mayo Clinic-Scottsdale at Scottsdale Sheraton Resort. Fri-Sat. Contact: Mayo Clinic-Scottsdale.

March 27-30—**15th Annual Primary Care Update.** Arizona Health Sciences Center, Tucson. Tues-Fri. Contact: Lynne Mascarella, (602) 626-7832.

March 29-30—**Clinical Reviews.** Mayo Clinic-Scottsdale at The Registry Resort, Scottsdale. Thurs-Fri. Contact: Mayo Clinic-Scottsdale.

March 31—**Nutrition Update for Primary Care Providers.** Arizona Health Sciences Center, Tucson. Sat. Contact: Lynne Mascarella, (602) 626-7832.

March 31—**Primary Management of Common Cardiovascular Conditions.** Mayo Clinic-Scottsdale at The Registry Resort, Scottsdale. Sat. Contact: Mayo Clinic-Scottsdale.

April 9-14—**Primary Care Update.** Tucson. Mon-Sat. Contact: Cristy Snow, (602) 626-7946.

April 20-21—**Series I—Coronary Heart Disease Update.** Medical Education Resources at La Posada Resort, Scottsdale. Fri-Sat. Contact: Deborah Helton, 1 (800) 421-3756.

June 22-24—**Thirteenth Annual Pediatrics in the Red Rocks.** American Academy of Pediatrics—Arizona Chapter at Los Abrigados, Sedona. Fri-Sun. Contact: Melanye Wrighton, (602) 230-1949.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

March 5-8—**18th Obstetric Anesthesia Conference.** Ohio State University Hospitals Department of Anesthesiology at Westin, Maui, Hawaii. Mon-Thurs. Contact: Arlene Rogers, 410 West 10th Ave, Columbus, OH 43210. (614) 293-8487.

March 9-13—**64th Congress of the International Anesthesia Research Society.** International Anesthesia Research Society at Sheraton Waikiki Hotel, Honolulu, Hawaii. Fri-Tues. Contact: IARS, 3645 Warrensville Center Rd, Cleveland, OH 44122-5280. (216) 295-1124.

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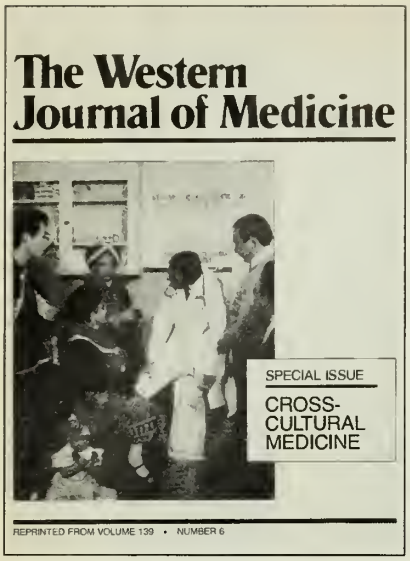

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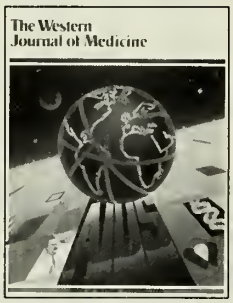
Women and Medicine

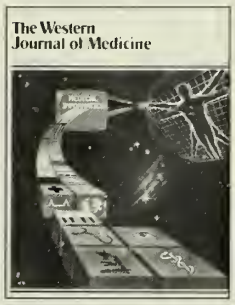
This special issue explores both the professional side of women in medicine and the diagnosis and treatment of women patients. Topics covered include liver disease, women and AIDS, heart disease, hysterectomy, PMS, ovarian cancer, and women physicians and organized medicine. Linda Hawes Clever, MD, Special Issue Editor, 1988.

AIDS—A Global Perspective



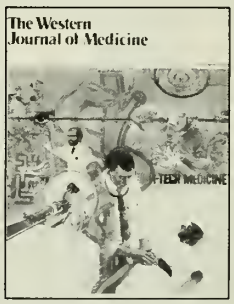
This issue, from the World Health Organization, considers the methods and limitations of AIDS case reporting and HIV serologic studies, summarizes modes of transmission, defines geographic patterns of spread, and examines the epidemiology of HIV infections by continent. Jonathan M. Mann, MD, Special Issue Editor, 1987.

Medical Informatics



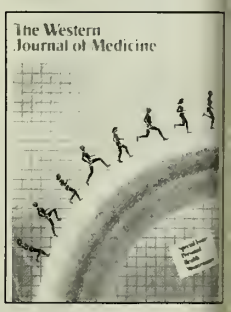
Medical Informatics explores the capabilities and potential capabilities of new electronic methods of collecting, processing, storing, analyzing, and using information to advance medical science and improve patient care. Marsden S. Blois, MD, Special Issue Editor, 1986.

High-Tech Medicine



This issue examines high-tech medicine as it pertains to patient care. Subjects include lasers in ophthalmology, cutaneous laser therapy, magnetic resonance imaging, organ transplantation, positron emission tomography, and modern molecular biology. R. Paul Robertson, MD, Special Issue Editor, 1985.

Personal Health Maintenance



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(Continued from Page 124)

March 17-18—**35th Postgraduate Assembly of Los Angeles County Society of Anesthesiologists.** Los Angeles County Society of Anesthesiologists at Sheraton Universal Hotel, Universal City. Sat-Sun. Contact: LACSA, PO Box 3465, Los Angeles 90051-1465. (213) 483-1581, ext 320.

March 24-25—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Newport Beach Marriott Hotel. Sat-Sun. 9 hrs. $125. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

May 17-20—**California Society of Anesthesiologists 1990 Annual Meeting.** California Society of Anesthesiologists at San Francisco Marriott. Thurs-Sun. 18 hrs. $175. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

May 29-June 3—**UCSD Anesthesiology Review Course.** UCSD at San Diego Princess, San Diego. Tues-Sun. Contact: UCSD.

CARDIOLOGY

February 21—**30th Annual Cardiovascular Symposium.** Enloe Hospital and Chico Community Hospital at Esplanade Building, Chico. Wed. 6 hrs. Contact: Linda Morgado, (916) 891-7300, ext 7375.

February 23-25—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Marquis Hotel, Palm Springs. Fri-Sun. Contact: Deborah Wilderson, MER, (800) 421-3756.

March 7-10—**Pulmonary Infections: Modern Diagnosis and Management.** California and Hawaii Thoracic Society at Royal Waikoloan, Kohala Coast, Hawaii. Wed-Sat. 12 hrs. $400. Contact: California Thoracic Society, 202 Fashion Lane, Ste 219, Tustin 92680. (714) 730-1944.

March 30-31—**Cardiology for the Clinician.** UCI at Long Beach. Fri-Sat. Contact: UCI.

April 2-11—**Cardiology for the Consultant: A Physicians' Retreat.** Scripps Clinic and Research Foundation at Rancho Santa Fe. 1½ weeks. 40 hrs. $900. Contact: Mary Ann Morris, 860 SW Scherer Rd, Lee's Summit, MO 64063. (816) 524-5780.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Avenue, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7186.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

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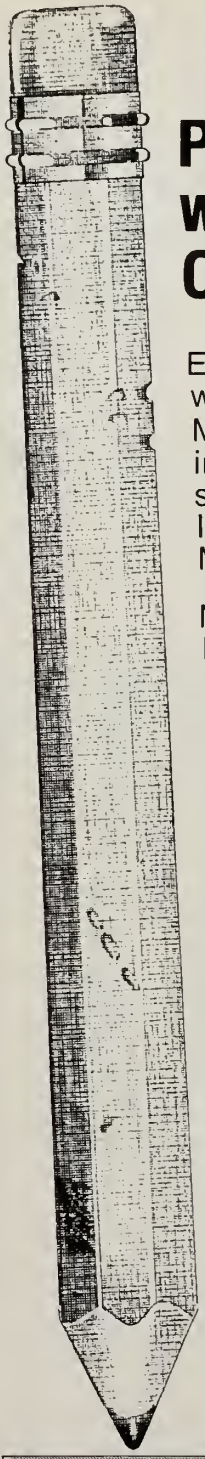

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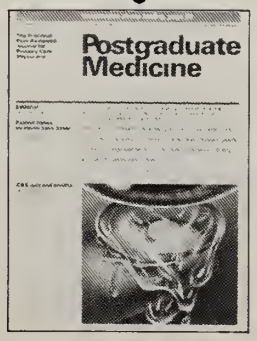

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CONTINUING MEDICAL EDUCATION

(Continued from Page 127)

April 28—**Current Concepts in Heart Disease.** Grossmont Hospital at Bahia Hotel, San Diego. Sat. 6 hrs. $100. Contact: Continuing Medical Education, Grossmont Hospital, PO Box 158, La Mesa 92044. (619) 589-4153.

May 4-5—**Series II—Arrhythmias: Interpretation, Diagnosis, and Management.** Medical Education Resources at Marriott Hotel, San Diego. Fri-Sat. Contact: MER, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4528. (303) 798-9682.

June 15-16—**Series IV—Cardiac Wellness and Rehabilitation.** Medical Education Resources at Hyatt Union Square, San Francisco. Fri-Sat. Contact: MER, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4528. (303) 798-9682.

June 22-23—**Series I—Coronary Heart Disease Update.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sat. Contact: MER, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4528. (303) 798-9682.

DERMATOLOGY

February 21-25—**Problems of the Aging Skin.** Stanford University at Las Vegas, Nevada. Wed-Sun. Contact: Paul Jacobs, Professor of Dermatology, Room R-144, Stanford 94305. (415) 723-7854.

June 8-9—**Southwestern Regional Cutaneous Flap Workshop.** UCLA. Fri-Sat. 15 hrs. Contact: Daniel E. Gormley, 412 W Carroll, Ste 207, Glendora 91740. (818) 963-7684.

EMERGENCY MEDICINE

February 17-20—**9th Annual Emergency Medicine and Acute Care: A Critical Appraisal Series 3.** Emergency Medical Abstracts at Las Vegas, Nevada. Sat-Tues. 20 hrs. Contact: Bob Cowsill, 6917 Royer Ave, West Hills 91307. (818) 884-8844.

February 18-21—**9th Annual Emergency Medicine and Acute Care: A Critical Appraisal Series 3.** Emergency Medical Abstracts at Los Angeles. Sun-Wed. 20 hrs. Contact: Bob Cowsill, 6917 Royer Ave, West Hills 91307. (818) 884-8844.

March 4-9—**11th Annual Mammoth Mountain Emergency Medicine Ski Conference.** UCI at Mammoth Lakes. Sun-Fri. 18 hrs. $395. Contact: Medical Conferences Inc, PO Box 52 B, Newport Beach 92662. (714) 650-4156.

March 19-23—**Emergency Medicine Symposium II.** UCSD at La Jolla Marriott Hotel. Mon-Fri. 32 hrs. Contact: UCSD.

March 21-23—**Advances in Emergency Medicine 1990.** UCSF at Mark Hopkins Hotel, San Francisco. Wed-Fri. 22 hrs. $425. Contact: UCSF.

April 7-14—**Cardiopulmonary Emergencies.** American Postgraduate Institute of Postgraduate Education and Scripps Memorial Hospital Encinitas at Poipu Beach Hotel & Waiohai Resort, Kauai, Hawaii. One week. Contact: Edith S. Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

April 19-22—**9th Annual Emergency Medicine and Acute Care: A Critical Appraisal, Series 3.** Emergency Medical Abstracts at San Francisco. Thurs-Sun. 20 hrs. Contact: Robert Cowsill, 6917 Royer Ave, West Hills 91307. (818) 884-8844.

May 7-11—**Emergency Medicine Symposium I: Cardiology, Pulmonary, Neurology.** UCSD at San Diego Hilton Beach and Tennis Resort. Mon-Fri. 32 hrs. $450. Contact: UCSD.

May 27-31—**Annual Scientific Assembly.** California Chapter of the American College of Emergency Physicians at Silverado Country Club, Napa. Sun-Thurs. 18 hrs. CAL/ACEP. (213) 374-4039.

June 25-29—**Emergency Medicine Symposium III: Pediatrics.** UCSD at San Diego Hilton Beach and Tennis Resort. Mon-Fri. 32 hrs. $450. Contact: UCSD.

INTERNAL MEDICINE

February 14-16—**23rd Annual Recent Advances in Neurology.** UCSF at Fairmont Hotel, San Francisco. Wed-Fri. 15 hrs. Contact: UCSF.

February 17-21—**Approaches to the Skull Base.** House Ear Institute at Marina Beach Hotel, Marina del Rey, Los Angeles. Sat-Wed. Contact: Antonio De La Cruz, MD, HEI, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

February 18-25—**Emergencies in Internal Medicine.** UCD at Lake Tahoe, Incline Village, Nevada. One week. 23 hrs. $410. Contact: UCD.

February 19-21—**Clinical Hematology and Oncology: 1990.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Wed. 24 hrs. $350. Contact: Bonny A. Mower, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

February 26-March 2—**Topics in Internal Medicine.** UCSD at Sheraton Harbor Island East Hotel, San Diego. Mon-Fri. 37 hrs. $475. Contact: Shirley Kolkey, 5665 Oberlin Dr, Ste 110, San Diego 92121. (619) 453-6222.

February 26-March 2—**Hyperbaric Medicine.** UCI/Memorial Medical Center. Mon-Fri. 36 hrs. $650. Contact: Celia Loney, (213) 595-3613.

February 28-March 2—**10th Annual Current Approaches to Radiation Oncology, Biology and Physics.** UCSF at Hotel Nikko, San Francisco. Wed-Fri. 18 hrs. $325. Contact: UCSF Radiation Oncology Course, c/o Crest International, 940 Emmett Ave, Ste 14, Belmont 94002. (415) 595-2704.

March 5-6—**Advanced TMJ Arthroscopy: Rationale, Treatment, and Management.** UCSD. Mon-Tues. Contact: UCSD.

March 7-8—**Advances in Endocrinology and Metabolism.** UCSF at Fairmont Hotel, San Francisco. Wed-Thurs. 14 hrs. $275. Contact: UCSF.

March 15-17—**5th International Conference on Monoclonal Antibody Immunoconjugates for Cancer.** UCSD at Sheraton Harbor Island East, San Diego. Thurs-Sat. Contact: UCSD.

March 24-29—**American Society of Clinical Pathologists and College of American Pathologists: 1990 Spring Meeting** at San Francisco Civic Auditorium. Sat-Thurs. Contact: ASCP/CAP National Meeting, PO Box 12075, Chicago, IL 60612-0075. (800) 621-4142.

April 18-20—**Advances in Infectious Diseases.** UCSD at Fairmont Hotel, San Francisco. Wed-Fri. 18 hrs. $380. Contact: UCSF.

April 21—**5th Annual Conference: New Treatments in Chronic Liver Disease.** Scripps Clinic and Research Foundation at Amphitheater of the Green Hospital, Scripps Clinic, La Jolla. Sat. $125. Contact: Bonny Mower, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 14-18—**Hyperbaric Medicine.** UCI/Memorial Medical Center. 36 hrs. $650. Contact: Celia Loney, (213) 595-3613.

May 18-20—**8th Symposium on Frontiers of Rheumatology.** Annenberg Center for Health Sciences. Fri-Sun. Contact: ACHS, 39000 Bob Hope Dr, Rancho Mirage 92270. (800) 321-3690.

May 26—**Fine Needle Aspiration Tutorials.** UCSF. Sat. 7 hrs. Contact: UCSF.

May 31-June 1—**Occupational and Environmental Medicine.** UCD at Capitol Plaza Holiday Inn, Sacramento. Thurs-Fri. Contact: UCD.

June 3—**Therapeutic Frontiers.** UCLA at Miramar Sheraton Hotel, Santa Monica. Sun. 6 hrs. $50. Contact: UCLA.

June 4-5—**TMJ Arthroscopy: Rationale, Treatment, and Management.** UCSD. Mon-Tues. Contact: UCSD.

OB/GYN

February 15-18—**45th Annual Obstetrical and Gynecological Assembly of Southern California.** Ob-Gyn Assembly of California at Beverly Hilton, Beverly Hills. Thurs-Sun. 22 hrs. Contact: Director of Medical Education, 5820 Wilshire Blvd, No. 500, Los Angeles 90036. (213) 937-5514.

March 21-23—**Advanced Fetal Heart Rate Monitoring.** UCI at Newport Marriott Hotel, Newport Beach. Wed-Fri. Contact: UCI.

March 22-24—**Geriatric Gynecology With Special Emphasis on Urinary Incontinence.** UCI at Palm Springs. Thurs-Sat. Contact: UCI.

April 19-20—**Prenatal Genetics Diagnosis and Fetal Therapy.** UCI at Red Lion Hotel, Costa Mesa. Thurs-Fri. Contact: UCI.

April 28—**Symposium on Gynecologic Oncology.** Scripps Clinic and Research Foundation at La Jolla. Sat. 7 hrs. Contact: Bonny Mower, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

June 1-3—**Advanced Fetal Heart Rate Monitoring.** UCI at Monterey Plaza Hotel. Fri-Sun. Contact: UCI.

OPHTHALMOLOGY

February 23-25—**American Academy of Ophthalmology Regional Update Course.** American Academy of Ophthalmology at Los Angeles. Fri-Sun. Contact: Gary Holland, MD, 655 Beach St, PO Box 7424, San Francisco 94120-7424. (415) 561-8500.

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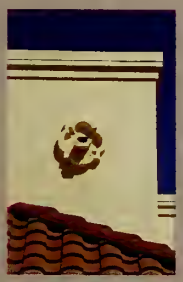

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March 31—**Ocular Inflammation.** Scripps Clinic and Research Foundation at La Jolla. Sat. 8 hrs. $90. Contact: Susan Buntjer, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

PEDIATRICS

February 16-18—**Pediatrics in Progress.** American Academy of Pediatrics at Hyatt Regency Embarcadero, San Francisco. Fri-Sun. 16 hrs. $220. Contact: AAP, CME Registration, PO Box 927, Elk Grove Village, IL 60009-0927. (800) 433-9016.

March 30-31—**Neurodevelopmental Assessment of 4-9 Year Old Children.** Children's Hospital Oakland. Fri-Sat. 12 hrs. $150. Contact: Kim Leadon, Children's Hospital Oakland, 747 52nd St, Oakland 94609. (415) 428-3021.

April 6-7—**Annual Ambulatory Pediatrics.** UCD at Hilton Inn, Sacramento. Fri-Sat. Contact: UCD.

April 19-20—**9th Annual Child Abuse.** UCD at Radisson Hotel, Sacramento. Thurs-Fri. Contact: UCD.

June 29-30—**Current Concepts in Pediatric Allergy and Otolaryngology.** Children's Hospital San Diego at Hyatt Islandia Hotel, San Diego. Fri-Sat. Contact: Continuing Medical Education Office, Children's Hospital, (619) 576-4072.

PSYCHIATRY

February 1990-May 1990—**Mental Research Institute Training Workshops at Mental Research Institute.** Contact: MRI, 555 Middlefield Rd, Palo Alto 94301. (415) 321-3055.

February 24-25—**Basic Hypnosis: A Hands-On Workshop.** Southern California Society of Clinical Hypnosis at Airport Marina Hotel, Los Angeles. Sat-Sun. 12 hrs. $295. Contact: Karnie Starrett, 10840 Queensland St, Los Angeles 90034. (213) 475-1260.

March 16-19—**Advanced Medical Hypnosis.** UCSD at The Inn Rancho Santa Fe. Fri-Sun. Contact: UCSD.

April 23-27—**Introduction to Medical Hypnosis.** UCSD at The Inn at Del Mar. Mon-Fri. Contact: UCSD.

April 28-29—**The Cutting Edge 1990—The Heart of the Matter: Helping Improve Relationships.** UCSD at La Jolla Marriott Hotel. Fri-Sat. 13 hrs. $300. Contact: Cass Jones, 7916 Convoy Court, San Diego 92111. (619) 565-9921.

RADIOLOGY

March 2-4—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Resort Hotel, Laguna Niguel. Fri-Sun. 18 hrs. $400. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 5-7—**Neuroradiology Update.** UCSD at Hotel del Coronado, San Diego. Mon-Wed. 18 hrs. $375. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 5-9—**Combined Neuroradiology Update and Magnetic Resonance Imaging.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 29 hrs. $450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 6-9—**Magnetic Resonance Imaging.** UCSD at Hotel del Coronado, San Diego. Tues-Fri. 23 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 6-9—**MRI for the Technologist: Symposium and Workshops.** UCSD at Hotel del Cornado, San Diego. Tues-Fri. 21 hrs. $275. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 16-18—**OB/GYN and Abdominal Sonography: Update 1989.** UCSF at Hyatt Regency, San Francisco. Fri-Sun. 15 hrs. $350. Contact: UCSF.

March 19-23—**33rd Annual Postgraduate Course in Diagnostic Radiology.** UCSF at Fairmont Hotel, San Francisco. Mon-Fri. 32 hrs. $515. Contact: UCSF.

March 26-30—**Diagnostic Imaging: 1990.** UCSF at Kauai, Hawaii. Mon-Fri. 23 hrs. $515. Contact: UCSF.

April 15-20—**10th Annual San Diego Residents Radiology Review Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 39 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 21—**Introduction to Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Sat. 8 hrs. $100. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

May 22-25—**CT and MRI in Body Imaging: A Comprehensive Course.** Tues-Fri. 15 hrs. $515. Contact: UCSF.

June 12-16—**Computer Assisted Radiology.** UCI at Anaheim Hilton Hotel. Tues-Sat. Contact: UCI.

July 19-22—**Radiology for Non-Radiologists.** UCSD at Hotel del Coronado, San Diego. Thurs-Sun. 26 hrs. $395. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 22-26—**Napa Valley Imaging Update: MRI 1990.** UCD at Silverado Country Club, Napa. Sun-Thurs. 17 hrs. $445. Contact: UCD.

July 23-25—**Musculoskeletal Imaging.** Hoag Memorial Hospital, Department of Radiology at Ritz-Carlton Resort Hotel, Laguna Niguel. Mon-Wed. 15 hrs. $350. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 26-29—**4th Annual Symposium on Magnetic Resonance Imaging.** Hoag Memorial Hospital, Department of Radiology at Ritz-Carlton Resort Hotel, Laguna Niguel. Thurs-Sun. 22 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

SURGERY

February 1990-December 1990—**Temporal Bone Surgical Dissection Courses: 1989.** House Ear Institute, 5 days per month. 53 hrs. $975. Contact: Antonio De la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

February 1990-June 1990—**Microsurgery Training Courses.** UCSD at Grossmont Hospital, La Mesa. 40 hrs. $1125. Contact: UCSD.

February 23—**Symposium on Retina and Vitreous Surgery.** White Memorial Medical Center New Otani Hotel and Garden, Los Angeles. Fri. 5 hrs. Contact: Farrah Arya, White Memorial Medical Center, 414 N Boyle Ave, Los Angeles 90033. (213) 269-0607.

March 15-18—**10th Annual San Diego Cardiothoracic Surgery Symposium: Pathophysiology and Techniques of Cardiopulmonary Bypass.** Cardiothoracic Research and Education Foundation at San Diego Marriott Hotel and Marina. Thurs-Sun. 17 hrs. $300. Contact: CREF, PO Box 33185, San Diego 92103. (619) 692-9115.

March 15-18—**Surgical Forum.** Society of Graduate Surgeons of Los Angeles County and USC Medical Center at Beverly Hilton, Beverly Hills. Thurs-Sun. Contact: Director, Society of Graduate Surgeons, 5820 Wilshire Blvd, Ste 500, Los Angeles 90036. (213) 937-5514.

March 23-24—**Aesthetic Surgery of the Face.** UCSF at San Francisco. Fri-Sat. 13 hrs. $750. Contact: UCSF.

April 7-8—**Automated Percutaneous Discectomy Workshop.** UCSF. Sat-Sun. 12 hrs. $800. Contact: UCSF.

April 19-20—**General Thoracic Surgery.** American College of Chest Physicians at Tropicana Hotel, Las Vegas. Thurs-Fri. 13 hrs. $275. Contact: ACCP, 911 Busse Hwy, Park Ridge, IL 60068. (708) 698-2200.

May 16-20—**12th Annual: Wound Management Workshop.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sun. 19 hrs. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

May 19—**Prosthetics-Orthotics Course.** UCD at UCD Medical Center, Sacramento. Sat. Contact: UCD.

June 17-22—**Anatomic Basis for Aesthetic Surgery: Hands-On Laboratory Course.** UCD at Hyatt Regency, Sacramento. Sun-Fri. Contact: UCD.

June 21-23—**7th Annual San Diego Meeting on Arthroscopic Surgery of the Shoulder.** Tri-City Medical Center at La Jolla Marriott Hotel. Thurs-Sat. Contact: James C. Esch, MD, 3905 Waring Rd, Oceanside 92056. (619) 598-0080.

July 17-21—**6th Annual Superficial Anatomy and Cutaneous Surgery.** UCSD at La Jolla Marriott. Tues-Sat. Contact: UCSD.

OF INTEREST TO ALL PHYSICIANS

February 12-17—**UCI Family Practice Refresher Course.** UCI at Newport Sheraton Hotel, Newport Beach. Mon-Sat. Contact: UCI.

February 17—**Clinical Epilepsy.** UCLA at Loews Santa Monica Beach Hotel. Sat. 7 hrs. $50. Contact: UCLA.

(Continued on Page 134)

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AIR FORCE

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CASE REPORTS

188 **Intracranial Tuberculoma Developing During Therapy for Tuberculous Meningitis**
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From the Departments of Internal Medicine and Clinical Investigation, Division of Infectious Diseases, Naval Hospital, San Diego, and the Department of Internal Medicine, Division of Infectious Diseases, National Naval Medical Center, Bethesda, Maryland.

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WALTER B. FORMAN, MD; DENICE SHEEHAN, RN; SUSAN CAPPELLI, RD; and BYRON COFFMAN, MD
From the Clinical Programs, University of New Mexico Cancer Center, Albuquerque, and the Saint Vincent Charity Hospital and Health Center, Cleveland.

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From the Pulmonary Disease Service, Department of Medicine, Letterman Army Medical Center, Presidio of San Francisco.

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Ms Dyer is a second-year medical student at the University of California, Davis, School of Medicine.

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ELLIOTT B. OPPENHEIM, MD
Dr Oppenheim is in private practice in Bellevue, Washington.

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★ **Official Journal of the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.**

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*The American Academy of Dermatology, the American Academy of Family Physicians, the American College of General Practitioners in Osteopathic Medicine and Surgery, the American Osteopathic Association, and the American Social Health Association.

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CONTINUING MEDICAL EDUCATION

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February 18-21—**Recent Advances in Geriatric Medicine: Strategies for Treating the Five Major Causes of Death and Disability in the '90s.** UCSD at Catamaran Hotel, San Diego. Sun-Wed. Contact: UCSD.

February 19-21—**10th Betty Ford Center Conference on Chemical Dependency.** Annenberg Center for Health Sciences and Betty Ford Center. Mon-Wed. Contact: Annenberg Center for Health Sciences at Eisenhower, 39000 Bob Hope Dr, Rancho Mirage 92270. (800) 321-3690.

February 19-23—**Physician Heal Thyself.** UCSD at San Diego Princess. Mon-Fri. 20 hrs. $350. Contact: UCSD.

February 22-24—**The Practicing Physician's Approach to Difficult Headache Patient.** Scripps Clinic and Research Foundation at Wyndham Hotel, Palm Springs. Thurs-Sat. 15 hrs. Contact: Idell Applebaum, 5252 N Western Ave, Chicago, IL 60625. (312) 878-5558.

February 24-25—**Advances in the Diagnosis and Treatment of Common Medical Problems.** UCSD at Sheraton Harbor Island East Hotel, San Diego. Sat-Sun. 12 hrs. $150. Contact: Shirley Kolkey, 5665 Oberlin Dr, Ste 110, San Diego 92121. (619) 453-6222.

March 2—**16th Annual Diabetes Symposium.** UCD at Hilton Inn, Sacramento. Fri. Contact: UCD.

March 2-7—**California Medical Association Annual Western Scientific Assembly.** California Medical Association at Disneyland Hotel, Anaheim. Fri-Wed. Contact: Sheri Sylvia, CMA, (415) 882-5184.

March 5-6—**Too Fat—Too Thin: Practical Concerns in Reaching Desirable Body Weight.** Mon-Tues. 12 hrs. $225. Contact: UCD.

March 5-8—**Environmental Illness and Injury.** University of Nevada-Reno at Hyatt Lake Tahoe Resort, Incline Village, Nevada. Mon-Thurs. 14 hrs. $275. Contact: University of Nevada, Continuing Education Department, Reno, NV 89557. (702) 784-4046.

March 9-10—**Diabetes Update.** UCSF at Fairmont Hotel, San Francisco. Fri-Sat. 10 hrs. $225. Contact: UCSF.

March 12-15—**Critical Care Medicine: 28th Annual Symposium.** USC at Las Vegas Hilton, Nevada. Mon-Thurs. 27 hrs. $585. Contact: USC.

March 13-18—**Wilderness Medicine: '90.** American College of Emergency Physicians at Squaw Valley, Lake Tahoe. Tues-Sun. 22 hrs. $395. Contact: Eugene Allred, PO Box 321, Yreka 96097. (916) 842-4667.

March 14—**Rationing Health Care.** Enloe Hospital at Esplanade Building, Chico. Wed. Contact: Linda Morgado, (916) 891-7300, ext. 7375.

March 19-22—**The Best Approach 1990: Effective, Efficient Strategies in Orthopaedics/Sports Medicine, Cardiology, Gynecology, and Infectious Disease.** Group Health Cooperative of Puget Sound at Intercontinental Hotel, Wailea, Maui, Hawaii. Mon-Thurs. 20 hrs. $325. Contact: GHCPS, CX-5, 201 16th Ave East, Seattle, WA 98112. (206) 326-6262.

March 24-25—**The Complaint of Insomnia in the Practice of Medicine: Scripps Clinic Sleep Update.** Scripps Clinic and Research Foundation. Sat-Sun. 11 hrs. $150. Contact: Susan Buntjer, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 28-30—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF at Hyatt Regency Hotel, San Francisco. Wed-Fri. 16 hrs. Contact: UCSF.

March 29-31—**Facing the Challenge.** Scripps Memorial Hospital at Hyatt Regency, La Jolla. Thurs-Sat. 21 hrs. $300. Contact: Nomi Feldman, 5665 Oberlin Dr, Ste 110, San Diego 92121. (619) 453-6222.

March 31-April 7—**Primary Care Medicine.** UCSF at Maui, Hawaii. One week. 20 hrs. $475. Contact: UCSF.

April 18-20—**40th Annual Course for Physicians in Family Practice: Practice in the 1990s.** Mount Zion Hospital and Medical Center, San Francisco. Wed-Fri. Contact: Mary Arnold, Mount Zion Hospital, PO Box 7921, San Francisco 94120. (415) 885-7270.

April 27—**Alzheimer's Update.** UCD at Beverly Garland Hotel, Sacramento. Fri. Contact: UCD.

June 3-8—**14th Annual Fingers to the Toes: Primary Care Orthopaedics.** UCD at Stanford Sierra Camp, Fallen Leaf Lake. Sun-Fri. Contact: UCD.

June 11-15—**UCI Family Practice Refresher Course.** Memorial/UCI Center for Health Education at Westin South Coast Plaza, Costa Mesa. Mon-Fri. 29 hrs. Contact: UCI.

(Continued on Page 135)

(Continued from Page 134)

June 21-23—**Nevada State Medical Association Annual Meeting.** Nevada State Medical Association at Hyatt Lake Tahoe, Nevada. Thurs-Sat. Contact: Nevada State Medical Association, 3660 Baker Lane, Reno, NV 89509. (702) 825-6788.

July 9-12—**Family Practice Board Review Course.** UCSF at Cathedral Hill Hotel, San Francisco. 25 hrs. Contact: Julia K. Engleton, Department of Family and Community Medicine, 400 Parnassus Ave, A-C9, San Francisco 94143-0900. (415) 476-1482.

July 9-13—**2nd Annual Marine Medicine.** UCSD at San Diego Princess. Mon-Fri. Contact: UCSD.

July 23-27—**4th Annual Sports Medicine.** UCSD at San Diego Princess. Mon-Fri. Contact: UCSD.

IDAHO

March 2-4—**Sex, Crime, and Violence—31st Annual Medical Winter Clinics.** Ada County Medical Society at Shore Lodge, McCall. Fri-Sun. 9 hrs. $100. Contact: Judy Barningham, Ada County Medical Society, PO Box 2668, Boise 83701. (208) 336-2930.

July 26-28—**Idaho Medical Association—Annual Meeting.** Sun Valley. Thurs-Sun. Contact: Idaho Medical Association, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

February 16-18—**Case Studies in Cardiology: A Cardiology Review for Clinicians.** Presbyterian Hospital, Albuquerque. Contact: Gilbert L. Raff, MD, Presbyterian Heart Institute, (505) 242-2796.

February 19-23—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Fri. Contact: American Educational Institute, (800) 354-3507.

February 23-25—**18th Annual New Mexico Thoracic Society Lung Disease Conference.** Santa Fe. Fri-Sun. Contact: Billie Dytzel, American Lung Association of New Mexico, 216 Truman, NE, Albuquerque 87118. (505) 265-0732.

February 26-March 3—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Sat. Contact: American Educational Institute, (800) 354-3507.

February 28-March 3—**New Mexico Metabolism Symposium.** Taos. Wed-Sat. Contact: Kathy Sickes, Lovelace Medical Foundation, 2441 Ridgecrest Dr, SE, Albuquerque 87108. (505) 262-7749.

March 5-9—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Fri. Contact: American Educational Institute, (800) 354-3507.

March 10—**Update: Pediatric Hematology.** Albuquerque. Contact: Alfred Florman, MD, New Mexico Pediatric Society, Surge Building, UNM SOM, Albuquerque 87131. (505) 277-5551.

March 12-16—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Fri. Contact: American Educational Institute, (800) 354-3507.

March 14-18—**Sports Medicine for the Primary Care Physician.** Durango, Colorado. Wed-Sun. Contact: Kathy Sickes, Lovelace Medical Foundation, 2441 Ridgecrest Dr, SE, Albuquerque 87108. (505) 262-7749.

March 15-18—**Medicine in Transition—Apathy or Renewal?** Albuquerque. Contact: John R. Graham, MD, Albuquerque Centre for Psychotherapy, 7521 Lantern Rd, NE, Albuquerque 87109. (505) 883-6959.

March 17—**Illness Behavior.** Psychiatric Medical Association of New Mexico at University of New Mexico, Department of Nursing and Pharmacy, Albuquerque. Fri. Contact: Psychiatric Medical Assn, (505) 841-3511.

March 19-23—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Fri. Contact: American Educational Institute, (800) 354-3507.

March 26-30—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Fri. Contact: American Educational Institute, (800) 354-3507.

March 30-31—**Can OB/GYN Survive Liability?** Albuquerque Convention Center. Fri-Sat. Contact: Mary R. Boning, Office of Medical Education and Research, Presbyterian Hospital, (505) 841-1225.

April 2-6—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Fri. Contact: American Educational Institute, (800) 354-3507.

April 9-13—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Fri. Contact: American Educational Institute, (800) 354-3507.

May 4-5—**103rd Annual Meeting of the New Mexico Medical Society.** Albuquerque. Fri-Sat. Contact: Glenn Taylor, New Mexico Medical Society, 7770 Jefferson, NE, Albuquerque 87109. (505) 828-0237.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

February 16-20—**Thirty-Fifth Annual Anesthesiology Update** (Sponsor: UUMC). Fri-Tues. Snowbird. Contact: (801) 581-6115.

February 17-21—**Thirty-First Annual Ob/Gyn Update** (Sponsor: UUMC). Sat-Wed. The Yarrow, Park City. Contact: (801) 581-5501.

February 21-23—**Physical Medicine and Rehabilitation Update** (Sponsor: UUMC). Wed-Fri. Park City. Contact: (801) 584-1226.

February 21-24—**Teratology for the Practitioner** (Sponsor: UUMC). Wed-Sat. Park City. Contact: (801) 581-5501.

February 21-24—**Pediatric Emergency Medicine** (Sponsor: UUMC). Wed-Sat. Salt Lake City Marriott, Salt Lake City. Contact: (801) 521-1315.

March 5-9—**Advances in Internal Medicine** (Sponsor: UUMC). Mon-Fri. Snowbird. Contact: (801) 581-8664.

(Continued on Page 138)

USING IT WON'T KILL YOU. NOT USING IT MIGHT.

Maybe you don't like using condoms. But if you're going to have sex, a latex condom with a spermicide is your best protection against the AIDS virus.

Use them every time, from start to finish, according to the manufacturers' directions. Because no one has ever been cured of AIDS. More than 40,000 Americans have already died from it.

And even if you don't like condoms, using them is definitely better than that.

HELP STOP AIDS. USE A CONDOM.

AMERICAN FOUNDATION FOR AIDS RESEARCH

Ad Council — A Public Service of This Publication & The Advertising Council

NATIONAL AIDS NETWORK

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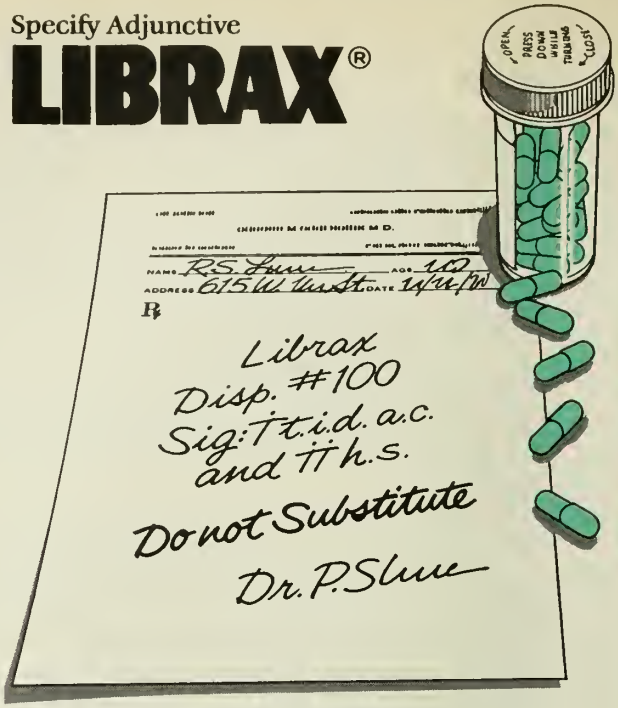
Specify Adjunctive

LIBRAX®



Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium bromide.

Please consult complete prescribing information, a summary of which follows:

* **Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e g*, operating machinery, driving).
Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.
As with all anticholinergics, inhibition of lactation may occur.
Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).
Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.
Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.
Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of chlordiazepoxide; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. After extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

P.I. 0288

ROCHE® **Roche Products**

Roche Products Inc.
Manati, Puerto Rico 00701

Be sure to specify Librax, "Do not Substitute" or your state's equivalent statement on your prescription.

In IBS,* when it's brain versus bowel,

IT'S TIME FOR THE PEACEMAKER.

In irritable bowel syndrome,* intestinal discomfort will often erupt in tandem with anxiety—launching a cycle of brain/bowel conflict. Make peace with Librax. Because of possible CNS effects, caution patients about activities requiring complete mental alertness.

*Librax has been evaluated as possibly effective as adjunctive therapy in the treatment of peptic ulcer and IBS.

Specify Adjunctive

LIBRAX®

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium bromide.

ROCHE®

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Please see summary of prescribing information on adjacent page.

(Continued from Page 135)

March 11-16—**Wilderness Medicine** (Sponsor: UUMC). Sun-Fri. Snowbird. Contact: (801) 581-8664.

May 3-4—**Ethics and Health** (Sponsor: UUMC). Thurs-Fri. University of Utah Health Science Center, Salt Lake City. Contact: (801) 581-8664.

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

February 21—**Neurology.** Seattle. Wed. Contact: Northwest Hospital, (206) 364-0500.

February 28—**AIDS Update.** Tacoma. Wed. Contact: CME Pierce County.

March 3—**AIDS Issues '90.** Kirkland. Sat. Contact: Evergreen Hospital, (206) 823-7599.

March 8-9—**Tacoma Academy of Internal Medicine Annual Review.** Tacoma. Thurs-Fri. Contact: CME Pierce County.

March 9—**Risk and Insurance Management for Physicians in Practice.** Seattle. Fri. Contact: VMMC.

March 9-10—**Advances in Clinical Cardiology.** Spokane. Fri-Sat. Contact: Spokane Society of Internal Medicine, (509) 448-2513.

March 15-16—**Primary Care Orthopaedics.** Seattle. Thurs-Fri. Contact: U/W.

March 21—**Drugs.** Seattle. Wed. Contact: Northwest Hospital, (206) 364-0500.

March 21-23—**Recent Advances in Cancer Detection.** Seattle. Wed-Fri. Contact: U/W.

March 26-April 6—**Physical Medicine and Rehabilitation.** Bellevue. Mon-Sun. Contact: U/W.

March 29-31—**Trauma and the Elderly.** Seattle. Thurs-Sat. Contact: U/W.

April 6—**A Day of Infectious Disease.** Seattle. Fri. Contact: VMMC.

April 12—**Psychopharmacology.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

April 13-14—**Tacoma Surgical Club.** Tacoma. Fri-Sat. Contact: (206) 627-7137.

April 13-14—**Sixth Annual Benton-Franklin County Medical Society Medical Seminar.** Tri-Cities. Fri-Sat. Contact: (509) 783-8616.

April 27—**Dermatology.** Tacoma. Fri. Contact: (206) 627-7137.

May 4-5—**Orthopedic Review.** Seattle. Fri-Sat. Contact: VMMC.

May 10—**Nutrition.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

May 10-11—**Aggressive Musculoskeletal and Spinal Evaluation, Treatment, and Rehabilitation.** Tacoma. Thurs-Fri. Contact: CME Pierce County.

May 18-19—**Applications of Doppler Ultrasound.** Seattle. Fri-Sat. Contact: VMMC.

June 8-9—**Common Anorectal Disorders: A Medical and Surgical Approach.** Seattle. Fri-Sat. Contact: VMMC.

June 14-15—**Orthopaedics.** Seattle. Thurs-Fri. Contact: Northwest Hospital, (206) 364-0500.

June 16—**AIDS Issues 1990.** Kirkland. Sat. Contact: Evergreen Hospital, (206) 823-7599.

June 25-26—**Advanced Cardiac Life Support.** Tacoma. Mon-Tues. Contact: CME Pierce County.

September 20—**Orthopedics.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

October 11—**Diabetes.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

November 8—**Pediatrics.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WYOMING

February 25-March 3—**Wyoming Academy of Family Physicians Annual Ski Meeting and Family Practice Update.** Jackson Hole. Sun-Sat. Contact: Hughes Planning, PO Box 3556, Jackson 83001. 1 (800) 342-7526.

June 14-16—**Wyoming Medical Society—Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sat. Contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. ◆

PHYSICIANS, A WEEKEND WITH THE RESERVE ISN'T JUST ANOTHER DAY AT THE OFFICE.

It's not just different in the Army Reserve, there are opportunities to explore other phases of medicine, to add knowledge, and to develop important administrative skills. There are enough different needs to fill right in your local Army Reserve unit to make a weekend a month exciting and rewarding.

Explore the possibilities. Call our officer counselor: **1-800-USA-ARMY**

ARMY RESERVE.
BE ALL YOU CAN BE.

Investigators' evaluations confirm hair growth in male pattern baldness of the vertex

ROGAINE® Topical Solution (minoxidil 2%) is the *first* prescription medication proved effective for male pattern baldness of the vertex. The effect on frontal baldness has not been adequately studied.

Evidence of growth was demonstrated by physician evaluations of 1,431 patients in 27 centers across the United States. Patients were placed on ROGAINE or placebo and evaluated each month for four months. Response was judged to be no growth, new vellus (baby) hair, or minimal, moderate, or dense growth.

In addition, after the placebo group was discontinued, continuous application of ROGAINE over an additional eight months was evaluated to determine if nonvellus growth could be sustained.

START OF STUDY

START OF STUDY

START OF STUDY

Examples of minimal, moderate, and dense growth as evaluated by investigators

© 1989 The Upjohn Company

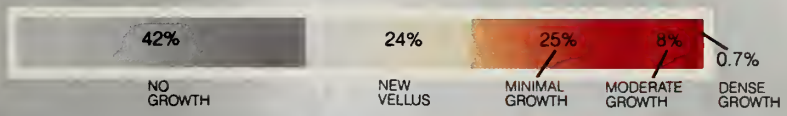
MINIMAL GROWTH

MODERATE GROWTH

DENSE GROWTH

Four-Month Phase
At the end of four months, 34% of 714 patients treated with ROGAINE were evaluated as showing minimal, moderate, or dense growth, while 20% of 717 patients showed minimal, moderate, or dense growth with placebo, a highly significant difference ($P<.0005$).

Rogaine (714)



Placebo (717)

Non-Placebo-Controlled Continuation Phase
After 12 months, dense growth was observed in 8% of the 619 patients treated with ROGAINE, moderate growth in 31%, and minimal growth in 37%. Approximately one fourth of patients showed only vellus hair growth or no growth.

Rogaine (619)

Compliance is Essential
The multicenter studies indicate that a period of *four months or longer* of daily b.i.d. applications of ROGAINE is usually necessary before evidence of hair growth is apparent. Hair growth continued to increase in study subjects over months 5 through 12.

Continuous use is necessary to maintain hair growth. Newly grown hair returns to the untreated state three to four months after cessation of therapy with ROGAINE.

Please see last page for brief summary of prescribing information.

Rogaine®
TOPICAL SOLUTION
minoxidil 2%

Upjohn
The Upjohn Company
Kalamazoo, MI 49001 USA

Rogaine® Rx

TOPICAL SOLUTION minoxidil 2%

INDICATIONS AND USAGE
Male pattern baldness (alopecia androgenetica) of the vertex of the scalp. No effect has been seen on frontal baldness. At least four months of treatment are generally required before evidence of hair growth can be expected; further growth continues through one year. The new growth is not permanent; cessation of treatment will lead to its loss in a few months.

CONTRAINDICATIONS
Hypersensitivity to minoxidil, propylene glycol or ethanol.

WARNINGS
1. Need for normal scalp: Before starting treatment, make sure that the patient has a normal, healthy scalp. Local abrasion or dermatitis may increase absorption and hence the risk of side effects.
2. Potential adverse effects: Although extensive use of topical minoxidil has not revealed evidence that enough minoxidil is absorbed to have systemic effects, greater absorption due to misuse, individual variability or unusual sensitivity could, at least theoretically, produce a systemic effect.
Experience with oral minoxidil has shown the following major cardiovascular effects (Review the package insert for LONITEN® Tablets for details):
—salt and water retention, generalized and local edema
—pericardial effusion, pericarditis, tamponade
—tachycardia
—increased incidence of angina or new onset of angina
Patients with underlying heart disease, including coronary artery disease and congestive heart failure, would be at particular risk of these potential effects. Additive effects could also emerge in patients being treated for hypertension.
Potential patients should have a history and physical, should be advised of potential risks and a risk/benefit decision should be made. Heart patients should realize that adverse effects may be especially serious. Alert patients to the possibility of tachycardia and fluid retention, and monitor for increased heart rate, weight gain or other systemic effects.

PRECAUTIONS
General Precautions: Monitor patients one month after starting ROGAINE and at least every six months afterward. Discontinue ROGAINE if systemic effects occur. The alcohol base will burn and irritate the eye. If ROGAINE reaches sensitive surfaces (eg, eye, abraded skin and mucous membranes) bathe with copious cool water.
Avoid inhaling the spray.
Do not use in conjunction with other topical agents such as corticosteroids, retinoids and petrolatum or agents that enhance percutaneous absorption. ROGAINE is for topical use only. Each mL contains 20 mg minoxidil and accidental ingestion could cause adverse systemic effects.
Decreased integrity of the epidermal barrier caused by inflammation or disease of the skin, eg, excoriations, psoriasis or severe sunburn, may increase minoxidil absorption.
Patient Information: A patient information leaflet is included with each package and in the full product information.
Drug Interactions: No drug interactions are known. Theoretically, absorbed minoxidil may potentiate orthostatic hypotension in patients taking guanethidine.
Carcinogenesis, Mutagenesis and Impairment of Fertility: No carcinogenicity was found with topical application. Oral administration may be associated with an increased incidence of malignant lymphomas in female mice and hepatic nodules in male mice. In rats, there was a dose-dependent reduction in conception rate.
Pregnancy Category C: ROGAINE should not be used by pregnant women.
Labor and Delivery: The effects are not known.
Nursing Mothers: ROGAINE should not be administered.
Pediatric Use: Safety and effectiveness have not been established under age 18.

ADVERSE REACTIONS
ROGAINE was used by 3510 patients in placebo-controlled trials. Except for dermatologic events, no individual reaction or reactions grouped by body systems appeared to be increased in the minoxidil-treated patients.
Respiratory (bronchitis, upper respiratory infection, sinusitis) 5.95%; **Dermatologic** (irritant or allergic contact dermatitis) 5.27%; **Gastrointestinal** (diarrhea, nausea, vomiting) 3.42%; **Neurology** (headache, dizziness, faintness, light-headedness) 2.56%; **Musculoskeletal** (fractures, back pain, tendinitis) 2.17%; **Cardiovascular** (edema, chest pain, blood pressure increases/decreases, palpitation, pulse rate increases/decreases) 1.28%; **Allergy** (non-specific allergic reactions, hives, allergic rhinitis, facial swelling and sensitivity) 1.03%; **Special Sensea** (conjunctivitis, ear infections, vertigo) 0.94%; **Metabolic-Nutritional** (edema, weight gain) 0.60%; **Urinary Tract** (urinary tract infections, renal calculi, urethritis) 0.46%; **Genital Tract** (prostatitis, epididymitis) 0.46%; **Psychiatric** (anxiety, depression, fatigue) 0.28%; **Hematology** (lymphadenopathy, thrombocytopenia) 0.23%; **Endocrine** 0.09%
Patients have been followed for up to 5 years and there has been no change in incidence or severity of reported reactions. Additional events reported since marketing include: eczema, hypertrichosis, local erythema, pruritus, dry skin/scalp flaking, sexual dysfunction, visual disturbances including decreased visual acuity, exacerbation of hair loss, alopecia.

DOSAGE AND ADMINISTRATION
Hair and scalp should be dry before application. 1 mL should be applied to the total affected areas twice daily. Total daily dose should not exceed 2 mL. If the fingertips are used to facilitate drug application, wash the hands afterwards.

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Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ANESTHESIA IN EMERGENCY MEDICINE—Edited by Glenn S. Vanstrum, MD, Clinical Instructor in Anesthesiology, University of California, San Diego, School of Medicine, and Staff Anesthesiologist, Sharp Memorial Hospital, San Diego. Little, Brown and Company, 34 Beacon St, Boston, MA 02108, 1989. 425 pages, $45 (paperback).

GROWTH REGULATION OF THYROID GLAND AND THYROID TUMORS—Vol 18 in Frontiers of Hormone Research—Edited by P. E. Goretzki and H. D. Röher, Düsseldorf. S. Karger AG, PO Box CH-4009, Basel, Switzerland, 1989. 159 pages. $110.

HYPERSENSITIVITY PNEUMONITIS: A CLINICAL APPROACH—Vol 23 in Progress in Respiration Research—Om P. Sharma, Los Angeles. S. Karger AG, PO Box CH-4009, Basel, Switzerland, 1989. 177 pages, $116.

PROBLEM BUILDINGS: BUILDING-ASSOCIATED ILLNESS AND THE SICK BUILDING SYNDROME—Edited by James E. Cone, MD, MPH, Assistant Clinical Professor, University of California, San Francisco, and Chief, Occupational Health Clinic, San Francisco General Hospital, and Michael J. Hodgson, MD, MPH, Director, Occupational and Environmental Medicine Program, and Assistant Professor of Medicine, Department of Medicine, University of Pittsburgh School of Medicine. Hanley & Belfus, Inc, 210 S 13th St, Philadelphia, PA 19107, 1989. 797 pages, $29.

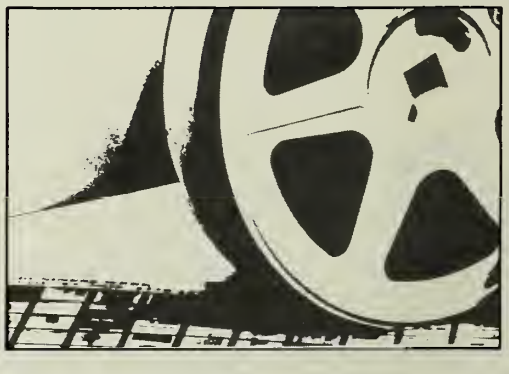
PROCEEDINGS OF XI EUROPEAN CONGRESS OF PERINATAL MEDICINE, Rome, April 10-13, 1988—Edited by E. V. Cosmi and G. C. Di Renzo, Institute of Gynaecology and Obstetrics, University of Perugia, Italy. Harwood Academic Publishers, PO Box 786, Cooper Station, New York, NY 10276, 1989. 867 pages, $89.

PUBLIC AND PROFESSIONAL ATTITUDES TOWARD AIDS PATIENTS—A NATIONAL DILEMMA—Cornell University Medical College Fifth Conference on Health Policy—Edited by David E. Rogers, MD, Walsh McDermott University Professor of Medicine, New York Hospital-Cornell Medical College, and Eli Ginzberg, PhD, Director, Conservation of Human Resources, and A. Barton Hepburn Professor Emeritus of Economics, Columbia University, New York. Westview Press, 5500 Central Ave, Boulder, CO 80301, 1989. 129 pages, $28.50.

SADDLEBACKS TO SCANNERS—THE FIRST 100 YEARS OF MEDICINE IN WASHINGTON STATE—Edited by Nancy Rockafellar, MA, and James W. Haviland, MD. Washington State Medical Association Education & Research Foundation, 900 United Airlines Bldg, 2033 Sixth Ave, Seattle, WA 98121. 294 pages, $37.50.

SUPPRESSOR B LYMPHOCYTES—Vol 1 in Immunology—R. V. Petrov, R. M. Khaitov, and B. V. Pinegin, Institute of Immunology, Ministry of Health of the USSR, Moscow. Harwood Academic Publishers, PO Box 786, Cooper Station, New York, NY 10276, 1988. 196 pages, $155.

This Publication is available in Microform.



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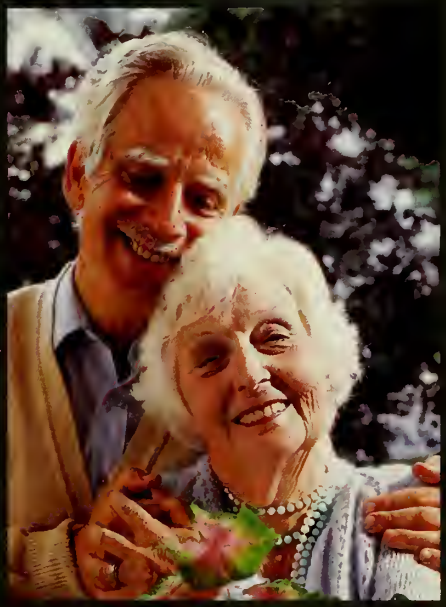

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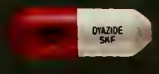

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'Dyazide' may be used alone or as an adjunct to other antihypertensive drugs; dosage adjustments may be necessary.

Contraindications: *Concomitant use with other potassium-sparing agents such as spironolactone or amiloride; potassium supplements (except in presence of severe hypokalemia); anuria, acute and chronic renal insufficiencies or significant renal impairment; hypersensitivity to drug or other sulfonamide-derived drugs; preexisting elevated serum potassium concentration.*

Warnings: *Abnormal elevation of serum potassium levels (greater than or equal to 5.5 mEq/liter) can occur with all potassium-conserving diuretic combinations, including 'Dyazide'. Hyperkalemia is more likely to occur in patients with renal impairment, diabetes (even without evidence of renal impairment), elderly or severely ill patients. Since uncorrected hyperkalemia may be fatal, serum potassium levels must be monitored at frequent intervals especially in patients first receiving 'Dyazide', when dosages are changed or with any illness that may influence renal function.*

If hyperkalemia is suspected, obtain an ECG and monitor serum potassium. If hyperkalemia develops, discontinue 'Dyazide' and initiate thiazide therapy if needed. Persistent hyperkalemia may require dialysis. Monitor serum electrolytes frequently in patients with mild renal dysfunction and in diabetic patients. In patients who may develop respiratory or metabolic acidosis, monitor serum electrolytes and acid/base balance frequently.

Precautions: *The bioavailability of the hydrochlorothiazide and triamterene components of 'Dyazide' is about 50% of the maximum obtainable with oral therapy. Theoretically, a patient transferred from therapy with hydrochlorothiazide with or without triamterene might show an increase in blood pressure, fluid retention, or change in serum potassium. Extensive clinical experience with 'Dyazide', however, suggests that these conditions have not been commonly observed in clinical practice. (See CLINICAL PHARMACOLOGY.) Use thiazides cautiously in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease; potassium depletion induced by the thiazide may be important in this connection; administer 'Dyazide' cautiously and be alert for such early signs of impending coma as confusion, drowsiness and tremor; if mental confusion increases, discontinue 'Dyazide' for a few days; attention must be given to other factors that may precipitate hepatic coma, such as blood in the gastrointestinal tract or preexisting potassium depletion. If patients develop hypokalemia, which is uncommon with 'Dyazide', increase potassium intake (i.e., with supplements or potassium-rich foods). If repeat determinations show serum potassium concentrations below 3.0 mEq/L, discontinue 'Dyazide' and initiate potassium chloride supplementation. Institute corrective measures cautiously and monitor serum potassium concentrations frequently, especially in patients receiving digitalis or those with a history of cardiac arrhythmias. Diuretics may aggravate existing electrolyte imbalances, especially at high dosages or in patients on salt-restricted diets. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Chloride replacement may be required in the treatment of metabolic acidosis. If dilutional hyponatremia develops, restrict water intake. In actual salt depletion, initiate sodium chloride replacement. Use 'Dyazide' cautiously in patients with a history of renal stone formation.*

If hyperkalemia develops when treating for hypokalemia, take corrective measures. Also discontinue 'Dyazide' and, if appropriate, substitute a thiazide diuretic until potassium levels return to normal. Do periodic BUN and serum creatinine determinations, especially in the elderly and in patients with suspected or confirmed renal insufficiency. Serum PBI levels may decrease without signs of thyroid disturbance. Discontinue thiazides before conducting parathyroid function tests.

Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine; therefore use cautiously in patients undergoing surgery. Monitor electrolytes in patients taking amphotericin B, corticosteroids or corticotropin concomitantly. Thiazides may potentiate the action of other antihypertensive drugs. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be needed. 'Dyazide' may raise the level of blood uric acid; dosage adjustments of antigout medication may be needed to control hyperuricemia and gout. The following agents given with triamterene may promote serum potassium accumulation and possibly result in hyperkalemia, especially in patients with renal insufficiency: blood from blood bank (may contain up to 30 mEq of potassium per liter of plasma or up to 65 mEq of potassium per liter of whole blood when stored for more than 10 days); low-salt milk (may contain up to 60 mEq of potassium per liter); potassium-containing medications (such as parenteral penicillin G potassium), and salt substitutes (most contain substantial amounts of potassium). Exchange resins, such as sodium polystyrene sulfonate, whether administered orally or rectally, reduce serum potassium concentrations by sodium replacement of the potassium; fluid retention may occur in some patients because of the increased sodium intake. Chronic or overuse of laxatives may reduce serum potassium concentrations by promoting excessive potassium loss from the intestinal tract; laxatives may interfere with the potassium-retaining effects of triamterene. The effectiveness of methenamine may be decreased when used concurrently with hydrochlorothiazide because of alkalinization of the urine. 'Dyazide' will interfere with the fluorescent measurement of quinidine.

There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if clearly needed. Thiazides and triamterene cross the placental barrier and appear in cord blood. The use of thiazides in pregnancy requires weighing the anticipated benefit against possible hazards, including fetal or neonatal jaundice, pancreatitis, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. Thiazides appear, and triamterene may appear, in breast milk. If use of the drug is essential, the patient should stop nursing. Safety and effectiveness in children have not been established.

Adverse Reactions: *The serious adverse effects associated with 'Dyazide' have commonly occurred in less than 0.1% of patients treated with this product. Anaphylaxis, rash, urticaria, photosensitivity, cardiac arrhythmias, postural hypotension, diabetes mellitus, hyperkalemia, hyperglycemia, glycosuria, hyperuricemia, hypokalemia, hyponatremia, acidosis, hypochloremia, jaundice and/or liver enzyme abnormalities, pancreatitis, nausea and vomiting, diarrhea, constipation, abdominal pain, acute renal failure, interstitial nephritis, renal stones composed primarily of triamterene, elevated BUN and serum creatinine, abnormal urinary sediment, leukopenia, thrombocytopenia and purpura, megaloblastic anemia, muscle cramps, weakness, fatigue, dizziness, headache, dry mouth, impotence, sialadenitis. Thiazides alone have been shown to cause the following additional adverse reactions: paresthesias, vertigo, xanthopsia, transient blurred vision, allergic pneumonitis, pulmonary edema, respiratory distress, necrotizing vasculitis, exacerbation of lupus, aplastic anemia, agranulocytosis, hemolytic anemia. In neonates and infants: thrombocytopenia and pancreatitis—rarely, in newborns whose mothers have received thiazides during pregnancy.*

Supplied: *Capsules containing 25 mg hydrochlorothiazide and 50 mg triamterene, in bottles of 1000 capsules; in Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.*

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Journal of the Arizona Medical Association

ARIZONA MEDICINE

February 1990, VOL. XLVII, No. 2

The Free Enterprise Spirit In Health Care: Is It Time To Extinguish the Flame?

Marshall B. Block, M.D.

Health care in America is our biggest unsolved problem. Eleven percent of our total domestic output is for health care and it is steadily rising. The cost per worker for health care increased almost 19% last year and will approach 17% this year. This places employers in a difficult competitive situation in the world marketplace. The Medicare program for the elderly will become the largest single component of the Federal budget by the year 2000. Despite this large expenditure for health care in America, thirty million people are uninsured and 55% of the population under the poverty level are not getting health care coverage. When attempts are made to either ration medical care or to expand coverage, there is an outcry from those directly affected by such maneuvers. For instance, when Governor Lamb of Colorado suggested that we limit our public spending for health care, i.e., ration it, the poor and the disadvantaged rose and complained that it would lead to a two tier health care system in the United States. When catastrophic health insurance was introduced just this year, it was the senior citizens who complained that they wer being asked to bear the cost of expansion of this program and they objected.

The *costs* of health care have been fueled by the introduction of complex and expensive technology, their increased utilization before their cost/benefit effects have been assessed, the aging of our population and the increasing costs of new diseases such as AIDS and drug dependency. Currently, *access* to health care in our country is determined by financial status. Those not of Medicare age who can afford health care have no difficulty. Those who fall below a financial standard are supported by society, either through the Medicaid program or in our state its alternative, the AHCCCS system. Those in between fend for themselves the best they can. Access can also be determined by health care contracts. They can minimize their financial exposure by insuring those that will potentially expend the least (young, healthy individuals) and exempt those that pose a greater risk (patients with chronic diseases like diabetes, AIDS, etc.).

The *allocation of resources* and the *quality* of the care obtained are also factors which depend on the vehicle used to purchase the care. Under a fee -for-service system, for instance, if the individual pays the physician directly, availability is unlimited. Yet, fee-for-service care received under a contract between an insurance company and the patient may have certain restrictions that may exclude pre-existing illnesses. Managed care plans, where the physician and insurance company are contractually related, may further alter the allocation of resources as well as their quality.

Health care delivery in the United States is currently ensconced in a capitalistic-free enterprise system which is not compatible with our society's goal of providing a basic level of care for all of its citizens in a fiscally responsible manner. If each year's premiums for coverage reflect the prior exposure of that individual, group or plan, how can the premium go anywhere but up unless we either decrease availability to care or restrict access to it? Which path is chosen depends on the vehicle used to finance the care. In indemnity plans, in order to control costs, *access* becomes the limiting factor, while in managed care plans *allocation of resources* is limited. The question that needs answering is whether we should be depending on fiscal balance sheets to reach medical decisions regarding access, allocation and quality of health care in the United States?

The entrepreneurial, buccaneer mode of health care delivery needs to be changed. By placing access,

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In This Issue:

- ICD Coding
- Young Physicians Section
- Is Geriatric Prevention a Reality?
- New Members
- Gleanings from ArMA Past
- Physicians in the News

The 1989 Interim AMA House of Delegates

The American Medical Association House of Delegates met in December and considered action on key issues affecting practicing physicians throughout the nation. Topics considered -- and policy decisions adopted -- included AIDS, drug abuse, drunk driving, and health care for the uninsured.

AMA President Alan R. Nelson, M.D., cited an impressive list of accomplishments in his keynote address to answer the proverbial question: "What does the AMA do for me?"

His list included:

- the defeat of mandatory assignment four times in the past three Congresses
- the fact that the AMA is the world's largest publisher of scientific information
- the defeat of expenditure targets in the budget bill
- the AMA's commitment to NIH funding to protect the stability and integrity of medical research in the U.S.
- the AMA's considerable activities in communicating medicine's story to the public
  - » weekly news releases to 3,000 reporters
  - » meeting with editorial boards
  - » American Medical Television reaches over 50,000 physicians and 800,000 lay people each month
  - » American Medical Radio News is used by 500 radio stations daily.

During its three-day session, the AMA House of Delegates took the following actions:

AIDS

The House approved a major policy update on the medical, legal, and social implications of AIDS and HIV infection. The Board report addressed a number of issues related to education, research, national policy, financing, media coverage, and the prevalence and incidence of AIDS:

- recommended contact-tracing and notification of needle partners
- recommended that the AMA Council on Medical Service study the cost of care for patients in each stage of HIV infection and estimate the number of people in each stage now and in five years.
- pledged ongoing support for funding for research, education, and patient care, as well as for alternatives to inpatient care.
- vowed to work with other physician groups, public health officials, and universities to advance training for primary care MDs and specialists.
- encouraged MDs to provide information to patients about HIV prevention and to become more involved in the care of HIV-infected patients.
- endorsed institutional indemnification of medical students and resident physicians infected as a result of patient contact.
- said AMA would consult with appropriate federal agencies and drug manufacturers about the expansion of AIDS drugs.
- urged MDs to take comprehensive and thorough sex and drug histories in a non-judgmental fashion.
- asked federal and state agencies to establish rigorous proficiency testing and quality control procedures for testing labs frequently and regularly.

Continued on page 17

OUR RATES ARE GETTING SMALLER AND SMALLER.

MICA is happy to announce that we have filed a request with the Department of Insurance to reduce our rates by 13.8%, effective April 1, 1990. This follows a 5% rate reduction in September, due to the passage of the Periodic Payments Bill. Together, these decreases will represent an 18.2% decrease in our rates within the last year.

There are many reasons for this significant decrease. First, MICA has had a favorable loss experience, both in the number and severity of claims. Other factors contributing to the decrease are MICA's thorough underwriting and efficient handling of claims, and our policyholders' participation in MICA's risk management programs.

Although different specialties will receive different decreases based on their loss experience, roughly 95% of all our policyholders will see a decrease of at least 13.4%. An Obstetrician's rates, for example, will be reduced by $9,440 since September and over $13,000 compared to last April. A complete listing of our proposed rates is available upon request.

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ICD-9 Coding: Receiving Optimum Reimbursement

Introduction

In our past three articles we discussed the importance of CPT and HCPCS coding. In this issue, we will direct your attention to the importance of International Classification of Disease coding, more commonly referred to as ICD coding.

When physicians code their services, they should think of ICD and CPT/HCPCS coding as interdependent. Without accurate coding your revenue will be affected. In the next few paragraphs we will demonstrate the importance of ICD coding and how it may affect the timeliness and reimbursement of your services.

A Word About ICD Coding

The U.S. Public Health Service and the Veterans Administration first introduced ICD coding in the 1950s as a way for hospitals to index their medical records for accurate storage and retrieval of diagnostic data. However, since that time the ICD coding system has improved due to nine revisions. In addition, hospitals and physicians now utilize the ICD coding system for recording diagnoses.

Today, we refer to ICD coding as ICD-9-CM, (International Classification of Disease, 9th revision, Clinical Modification). ICD-9-CM coding is now the most accurate source of diagnosis coding. Only recently, however, has it become such an integral part of reimbursement for medical services.

The Contents of the ICD-9-CM Volumes I, II, III

The contents of the ICD-9-CM volume set are arranged so that referencing the specific illness or injury is easy. However, one must develop a working knowledge of the contents to ensure optimum coding accuracy. Below, you will find a brief description of Volumes I, II and III.

Volume I contains the tabular (numeric) listing of the ICD-9-CM codes. In contrast, Volume II contains the alphabetical listing of the classification of diseases. Volume III contains codes specifically for hospital and other facility charges. Volume III also contains both the alpha and tabular codes.

It is always recommended when coding for physician services, one should refer to both Volumes I and II. For example, many physicians use the ICD-9-CM code 401, found in Volume I, for Hypertension. However, to locate a more specific ICD-9-CM code for Hypertension, one must look in Volume II for the code corresponding to the specific type of Hypertension. By referencing both volumes, you are more likely to choose the most accurate code.

New Legislation Concerning ICD-9-CM Coding

On April 1, 1989, a new law governing the submission of diagnosis codes on all HCFA 1500 forms or bills submitted to Medicare became effective. There was a two month grace period extended to those needing to make the appropriate changes in their coding operations. This new law affected both electronic and paper claims. Furthermore, the ICD-9 code should reflect the highest level of diagnosis specificity possible. For example, use five digit ICD-9 codes before using four digit codes.

All Medicare claims must contain the narrative description as well as the corresponding ICD-9 code. If this procedure is not followed, Medicare will deny the claim and request the ICD-9 code and narrative description.

Do not use "Rule-out" or "Possible" as if they are established illnesses or conditions. Many insurance carriers will not pay on claims that reflect this diagnosis because it does not state a specific illness.

How the Most Accurate ICD-9-CM Code Will Ensure Optimum Reimbursement

Never before has matching your procedure code with the proper ICD code been so important. The following examples will demonstrate the interdependency of ICD-9-CM and CPT/HCPCS coding.

Example #1

Appropriate matching of service and diagnosis coding:

ICD-9-CM code 250.0
Diabetes Mellitus w/o complication

90050- Office visit
ICD-9-CM- 250.0

81000- Urinalysis
ICD-9-CM- 250.0

93784- Ambulatory Blood Pressure Monitoring
ICD-9-CM- 250.0

Example #2

Inappropriate matching of service and diagnosis coding:

ICD-9-CM code 812.0
Fracture of Humerus upper end closed

(Same patient as in example #1.)
73060- Radiologic exam
Humerus/one view

ICD-9-CM- 250.0

81000- Urinalysis
ICD-9-CM- 812.0

93784-Blood Pressure Monitoring
ICD-9-CM- 812.0

Upon receipt of Example #2, an insurance company may question the necessity of the Urinalysis and Blood Pressure monitoring with the 812.0 ICD-9-CM code. Thus, the claim may be denied or pended for medical necessity.

Every claim should be reviewed before being submitted to the insurance carrier. By reviewing the claim before submitting it to the insurance carrier, you can catch errors in coding. It is more efficient for the person coding the claim to spend a little more time pre-screening the claim form than to spend time correcting the claim two or three months later.

Summary

As demonstrated in this article, the ICD-9-CM codes are an integral part of the coding system. A fourth edition of the ICD-9-CM coding booklets is due to come out in the next couple of years. It will be important to purchase the new edition so that your coding is current and accurate. Reimbursement for your services is based solely on the way you code. Therefore, establishing a working knowledge of ICD-9-CM coding will ensure optimum reimbursement. ■

Claire Miller and Joan Miller are President and Chief Financial Officer of SysteMedical Management, Inc., a medical practice management firm located in Mesa, Arizona. They can be reached at (602) 833-4855.

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Young Physicians Section

Beginning with this issue of Arizona Medicine, concerns of Young Physicians will be addressed in a quarterly format. Physicians are encouraged to participate with articles, letters to the editor, comments and suggestions.

Did you know that there are over 2600 licensed practicing physicians that meet the criteria of "young physician" (age, 40 or under or in practice less than 5 years)? This number when coupled with residents and students makes up approximately 1/3 of the physicians in the state. These numbers are significant in that they represent a base that will shape organized medicine for this decade and beyond. Clearly, organized medicine is evolving; the perception of those involved in organized medicine is changing. ArMA's President, Dr. Mark Ivey is one of the youngest presidents to occupy the office. The Young Physician Section was formed with the realization the younger physicians are the life blood of organized medicine as a whole. One fact remains clear, health care delivery is changing. The only other variable is WHO will participate in that change. Certainly, it is the intent of the YPS-Governing Council to insure that young physicians get involved; that they have impact in the shaping of medicine. Impact equals participation and participation equals membership. It is now more important than ever with the increasing encroachment on medical practice that physicians of all disciplines effectively join forces to combat the erosion of their profession. There are a number of reasons to join organized medicine, the benefits are many. More importantly however, are the reasons not to be on sidelines. Sidelines are for spectators and medicine is not a spectator sport.

1. I owe it to myself, my practice and to my colleagues to support organized medicine to move forward at the regional and national levels.
2. It takes strength in numbers and collective action to achieve anything worthwhile.
   Other groups and agencies have effectively organized to change health care delivery. By participating in organized medicine I can impact the profession.
3. The regular meetings and conventions I attend bring me ideas and critical information I could obtain no other way. Continuing Medical Education provides professional growth and a method of sharing information.
4. I have many friends among the members—people I enjoy being with for friendship's sake, as well as for professional business reasons. My life is richer and more rewarding through belonging.
5. Through the committees and association activities I am able to contribute, to do my part in moving the industry forward for the common good.
6. Legislatively—I can make my voice heard on issues affecting medicine.
7. The cost of belonging is small compared to what I get in return—extremely low rent for the space I occupy in the industry.
8. Even when other problems command my full attention, the officers, directors and Association staff keep working in my interest.

David R. Nielsen, M.D.
Chairman, Young Physicians Governing Council

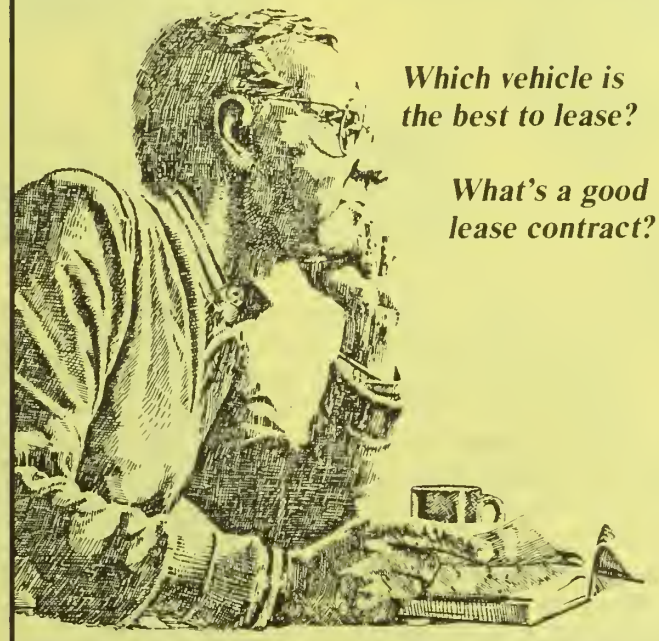
From the Editor
Continued from page 1

allocation and quality of health care delivery in the control of a health care consortium we can more closely evaluate and assess cost/benefit outlays. For instance, the value of newer technology and therapy must be extensively assessed before entering the marketplace. The use of laser angioplasty is presently mushrooming before we even know its indications and whether it has long-term value. Balloon angioplasty is likewise being extensively performed without its longer term ramifications known. The use of erythropoietin, a biogenetic product which enhances red cell production, is being implemented in patients on chronic renal dialysis at a cost of close to eight hundred million dollars a year! Will raising the hematocrit from 25% to 30% i n patients who are already disabledbe worth the cost ? The use of liver transplantation is a burgeoning business at a cost close to one hundred and fifty thousand dollars per transplant. Could this money be better spent immunizing the population against hepatitis-B? The dismantling of hospitals and the establishment of outpatient facilities that has recently occurred was not well thought out ahead of time. Although outpatient care seemed cheaper, after factoring in the cost to duplicate and triplicate services, the ultimate outcome appears to be far different. Furthermore, the outcome of medical care in general is largely unknown. Do physicians who have lower hospitalization rates practice better medicine than those who admit their patients frequently to the hospital? What is the ultimate mortality and morbidity of these two groups of patients?

Although we don't have answers to many of the above questions, we cannot wait for their resolution before somehow coming to grips with the deficiencies of our current health care system. Some practical solutions, albeit interim, need to be drafted and put into place until we have answers. Attempts by municipalities to prioritize the health care needs of their citizens and structure a program within their current budgetary restraints appears to be a step in the right direction. A "safety net" of care for all of our citizens could thus be developed as needs and costs allow. Increased coverage could be added either by the patients themselves, their employers or society in general. I feel that it is time that, as physicians, we address the bigger issue facing our society and look beyond our own parochial interests in helping to resolve this difficulty. What more important goal could we have as a healing profession than to cure this major wound affecting our fellow citizens? Shouldn't our organizations, be it local, state, national, general or subspecialty, be hearing from us to make certain they are aware of our wishes? Should we not be outspoken and press our position to our elected representatives and to the local and national media? What better way is there for us to redeem ourselves as a caring profession than to promote such a position! ■

Marshall B. Block, M.D.
Editor

Important Questions?



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Is Geriatric Prevention a Reality?

There are many reasons why prevention needs to become a reality for our older patients, including economic and humanitarian considerations, the promise of improved quality of life, as well as increased function and independence through expansion of the "health span." A greater proportion of our patients will continue to survive into very old age. Preventive geriatrics is a concept whose time has come.

A number of barriers make it difficult for physicians to practice preventive geriatrics. Third party reimbursement is not sufficient as Medicare continues to be acute care and crisis oriented. Less than two percent of all health dollar expenditures for the elderly is directed toward prevention. Although they feel it is of value, the majority of physicians do not feel competent at providing counseling. More research is needed on the cost-effectiveness of all preventive interventions and the appropriateness of "age-based" cut-offs for specific interventions. And, the majority of physicians still feel that there is little professional gratification in providing preventive care.

Solutions to overcome many of these barriers are emerging. Medicare coverage of periodic preventive health visits is available through an experimental program in North Carolina. Recently published recommendations of the U.S. Preventive Services Task Force provide physicians with a comprehensive spectrum of effective prevention activities and conclude that low-cost office-based counseling is the most effective type of intervention. Physician attitudes are being affected by preventive geriatric training in medical schools, residency programs, and through continuing medical education. The University of Arizona College of Medicine introduces clinical preventive medicine to students in their first year, and provides clinical preventive experiences during the third and fourth year. A model preventive geriatrics curriculum will soon be implemented for Preventive Medicine Residents. A biannual geriatric update and review course emphasizing prevention education for practicing physicians is also sponsored by the College. We are also currently involved in a number of longitudinal and community-based research projects on healthy aging such as the AURA Health Watch Study in Sun Cities, Project AGE WELL, and Health-Peers. These and other model community-based health promotion programs throughout the country have shown how community coalitions and teams can coordinate with physicians to deliver preventive services to the elderly in innovative settings such as retirement communities, church wellness programs, and the worksite. These combined efforts may succeed in decreasing hypertension, unsafe medication use, physical inactivity, osteoporosis, and social isolation -- modern plagues affecting the elderly. Physicians need to design more efficient ways of using ancillary staff and community resources in their delivery of preventive care. Older adults must be encouraged to practice self-responsibility in their health care habits and be pro-active. This may require incentives such as risk-rated health insurance with premiums based on the individual's behavior risk profile and/or willingness to reduce unhealthy behaviors. The routine emphasis of non-pharmacological treatments (such as stress reduction, nutrition, and exercise) over pharmacological efforts will help encourage a preventive mind-set among both physicians and patients.

Despite accumulating evidence that health promotion and disease prevention interventions can improve quality of life and decrease morbidity, routine preventive care is not yet a reality for most older adults.

Older adults are receptive to preventive interventions through ther personal physician and community programs, and have the most to benefit in terms of delaying the onset of dysfunction and disability.

Evan Kligman, M.D.
Assistant Professor
Family and Community Medicine
College of Medicine

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Institute of Medicine
Far Eastern University - 1962

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Scottsdale
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University Xochicalo - 1979

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Medicine - Nashville - 1984
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Internal Medicine, Tucson
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Gleanings from the ArMA Past

In 1892 -- the year of founding of the Arizona Medical Association, the following advances in medicine were noted on a national level:

- Sternberg first describes viral neutralizing antibodies (vaccinia).
- Opening of New York City Bacteriological Laboratory
- Smith and Kilbourne demonstrate tick transmission of bovine piroplasmosis (Texas fever).
- Halstead successfully ligates first portion of the subclavian artery.
- Frank Hartley resects gasserian ganglion for trigeminal neuralgia.
- Sedwick emphasizes necessity of fly-control for prevention of typhoid fever.

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Reference

Two Centuries of American Medicine; Bordley and Harvey, W.B. Saunders: 1976, pg. 786

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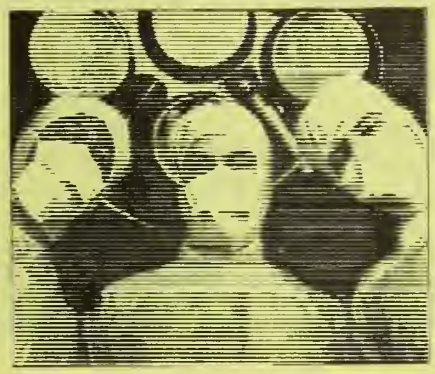

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Physicians in the News

James Levi, M.D.

For the past three years **James Levi, M.D.,** has kept the pavement hot pursuing his love for cars and car racing. The Tucson orthopedic surgeon began tinkering with cars as a teenager and drag raced the 1932 and 1937 Ford Coupes. Today he successfully races in a Formula Ford 2000, also known as a Formula Continental which enjoys a top speed of 130 mph.

He recently competed in the Sports Car Club of America (SCCA) Fall Series in the Formula Continental category. This category is new to amateur racing and is just beginning to become popular. He participated in four of the five events, finishing first in three races and second in the other event.

Before the Formula Continental, Dr. Levi was successful driving another Formula Ford, the 960-pound LOLA. Participating in the Club Ford category, in May 1987 he won his first regional race at Firebird International Raceway in Phoenix. He continued on to place first in the grueling hour-long Enduro races in 1987 and 1988, taking second in the state in 1988. He also placed second in the Eloy Grand Prix last April.

Dr. Levi not only participates as a driver at the track, but he also volunteers his skills as a track physician for various amateur and professional events. He will be working as one of a dozen track physicians at the Iceberg Grand Prix March 9, 10 and 11 in Phoenix and also for the Indy car race at Phoenix International Raceway in April.

In addition to his racing fame, on the professional front, he is the president-elect of the Arizona Orthopedic Society and has presided over numerous orthopedic organizations and hospital divisions over the years. Dr. Levi is particularly interested in knee injuries and arthroscopy. He is with Associated Orthopedic Surgeons, P.C. and practices surgery at the orthopedic sections of TMC and Kino Hospital. His group leads the Kino orthopedics division.

Dr. Levi presently is preparing for races at Firebird in January and February and the Eloy Grand Prix in April which is known as the "Third Longest Running Street Race in the World."

Anthony Vuturo, M.D., has been appointed associate dean for health affairs for The University of Arizona College of Medicine to strengthen the college's relations with a wide variety of community and government organizations.

Dr. Vuturo is head of the UA Department of Family and Community Medicine and continues in that position.

As associate dean for health affairs, Dr. Vuturo oversees continuing medical education courses and helps coordinate a wide variety of educational, clinical and community hospitals throughout the state, as well as with other agencies and organizations.

"I wanted someone with a broad understanding of the entire College of Medicine, the state and the University—someone with vision who can seize new opportunities," says James E. Dalen, M.D., UA vice provost for medical affairs and dean of the College of Medicine. "As a state medical school, we have an

obligation to serve Arizona in as many creative ways as possible; Dr. Vuturo will help us complete t hat mandate."

"This appointment provides an exciting opportunity to ensure that the state's only medical school continues developing important relations throughout Arizona and elsewhere," Dr. Vuturo says. "We want to extend our vision to governments around the world in building significant relationships in research, education and service."

Dr. Vuturo, 49, joined the UA faculty in 1979 as professor and head of family and community medicine. As department head, he supervises approximately 1,000 faculty and staff members, oversees the training of medical students in 38 different locations throughout Arizona, and manages a group practice of 65 physicians and 12 ambulatory care facilities in both urban and rural settings. Also, he supervises UA research and clinical outreach projects in 10 different countries around the world.

Dr. Vuturo recently became the seventh recipient of the Thomas W. Johnson Award for outstanding achievement in family practice, chosen from physicians worldwide. Since the founding of the family practice medical specialty in 1968, only six Johnson Awards have been presented.

Anthony F. Futuro, M.D., displays Thomas W. Johnson Award

Dr. Vuturo is the newly appointed associate dean for health affairs for the College of Medicine and head of the family and community medicine department.

Dr. Vuturo received the Johnson Award from the American Academy of Family Physicians at the Academy's annual convention in Los Angeles this fall. The award recognizes outstanding achievement in family practice education on the undergraduate, graduate and continuing education levels. Specifically, the Academy cited Vuturo's pioneering work in international outreach, managed care and geriatric training in his selection.

After graduating from the University of Kentucky College of Medicine and completing his residency, Vuturo served as director of preventive medicine for the Department of Health, Education and Welfare/U.S. Civil Administration in Japan's Ryukyu Islands. Vuturo earned a master's degree in public health from Harvard University and has completed the Executive Development Program of the Massachusetts Institute of Technology.

Selma E. Targovnik, M.D., and Jerome Targovnik, M.D.

Selma E. Targovnik, M.D., and Jerome Targovnik, M.D., have been presented with the prestigious Maimonides Award, by Leonard Sherman, National President of the American Society for Technion-Israel Institute of Technology.

The Targovniks were chosen to be the honorees because of their concern and commitment for the well-being of people in the community and in the world around them. Jerry has been President of the Arizona

Affiliate of the American Diabetes Association. He is spearheading an educational drive for the prevention and early treatment of diabetes in the Hispanic, Hopi and Navajo communities. Jerry's research is focused in the field of pancreatic transplantation and reversal is focused in the field of pancreatic transplantation and reversal of diabetic complications. Selma is an eclectic activist. She is involved with Beth El Congregation, the State Board of the A.C.L.U. and the American Cancer Society. This year, she was written up in *Trends* magazine as an "Image Maker."

The Technion-Israel Institute of Technology is known for its achievements in the sciences, engineering, technology, and medicine. The Institute is similar to M.I.T. and Cal Tech and is ranked among the top universities of its kind in the world -- and is the keystone of Israel's security, technological advances and general well-being.

The University, in addition, sponsors a very "people-oriented" program that strives to help disadvantaged youngsters to fulfill themselves. The program is known as "PERACH"... a word that means flower in Hebrew and is an acronym for "instructional programs." Technion students, on a one-to-one basis, spend several hours each week with disadvantaged youngsters. They serve as role models for the kids they befriend—motivating them to achieve academic success as well as fostering good social skills.

The Targovniks have made a commitment to this vital Technion project in honor of their daughters, Nina and Diane, and in memory of their son, Labe. ■

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1989 Interim
Continued from page 2

- reaffirmed its commitment to mandatory testing of inmates in federal and state prisons and supported mandatory testing of all newborns in high prevalence areas.

In other AIDS- related actions, the House:

- encouraged state legislation to establish requirements for reporting and case follow-up for serious contagious disease, including HIV infction.
- requested that the Food and Drug Administration address the problem of readable instructions for condoms.
- recommended that the FDA not allow home test kits for HIV.

Drug Abuse in the United States

The House considered a Board report and several resolutions related to drug abuse. The report states that America's drug epidemic has evolved in recent years from an urban plight to a national crisis. The Board pledged its continuing involvement in programs to alert physicians and the public to the dimensions of the problem and the most promising solutions. The report recommended that the AMA:

- Cooperate in activities of organizations such as the National Association for Perinatal Addiction Research and Education (NAPARE) in fostering education, research, prevention, and treatment of maternal drug and alcohol use.
- Encourage the development of model alcohol and drug treatment programs, complete with an evaluation component, that are designed to meet the special needs of pregnant women through a comprehensive array of essential services.
- Urge physicians to routinely screen all pregnant women, and those of childbearing age for drug and alcohol use, and to follow-up positive screens with appropriate interventions and referrals.
- Pursue the development of educational materials for physicians and the public on prevention, diagnosis, and treatment of perinatal addiction. In this regard, the Board encourages further collaboration with the Partnership for a Drug-free America in delivering appropriate messages to health professionals and the public on the risks and ramifications of perinatal drug and alcohol use.
- Urge the National Institute on Drug Abuse, the National Institute on Alcohol Abuse and Alcoholism, and the Federal Office for Substance Abuse Prevention to continue to support research and intervention strategies.
- Urge that public policy be predicated on the understanding that alcoholism and drug dependence are diseases characterized by compulsive use in the face of adverse consequences.
- Affirm the concept that substance abuse is a disease and develop model legislation to appropriately address perinatal addiction as a disease, bearing in mind physicians' concern for the health of the mother, the fetus, and resultant offspring.
- Call for better coordination of research, prevention, and intervention services for women and infants at risk for both HIV infection and perinatal addiction.

In a related action, the House adopted a resolution, entitled "Substance Abuse as a Public Health Hazard," that called upon the AMA to:

- recognize that substance abuse is the major health problem in the United States today and that its solution requires a multifaceted approach
- declare substance abuse its number one public health priority
- take a positive stance as a leader in matters concerning substance abuse
- study innovative approaches to the elimination of substance abuse dependencies and their resultant street crime, including approaches which have been used in other nations.

Prevention of Drunk Driving

The House adopted a resolution introduced by the Young Physicians Section that addressed the issue of the involvement of alcohol as a leading cause of morbidity and mortality in motor vehicle accidents. The House voted to:

- encourage state medical societies to urge their state legislators to adopt a blood alcohol level of 0.05 percent as per se illegal for driving
- work with Congress to make federal highway funds to states contingent upon state adoption of a blood alcohol level of 0.05 percent as per se illegal for driving.

Health Insurance Coverage for Uninsured

The House adopted a resolution that addressed the problem of having an estimated 37 million Americans without health insurance. Introduced by the American Academy of Family Physicians, the resolution called upon the AMA to reaffirm its support for ensuring access to health care for the uninsured:

- through a combination of employer-sponsored coverage
- other private approaches such as risk pools and the AMA proposed restructuring of Medicaid and Medicare programs

The resolution also asked the AMA to aggressively pursue implementation of a program ensuring health care access for the uninsured as a high legislative priority beginning in the 101st Congress.

Dependent Uninsured Coverage

In a related action, the House approved a resolution, introduced by the Hospital Medical Staff Section, calling for an AMA study of the health insurance coverage for the uninsured "dependent" population.

Billing for Cross-coverage

A number of resolutions addressed physician dissatisfaction with the referral of Medicare, Medicaid, and most private payors to allow solo practitioners to bill for services provided by covering physicians.

The House approved a policy calling on the AMA:

"to pursue all appropriate legisla tive, regulatory, and administrativ means to amend or eliminate th inappropriate enforcement of th Social Security Act and/or Medicar regulations in order to make it pos sible for physicians in solo or grou practice to bill and receive paymer for professional services to the Medicare patients rendered by co leagues who provide them wit traditional short-term coverage."

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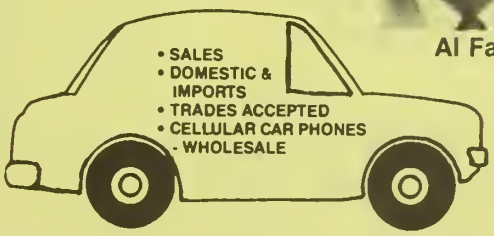

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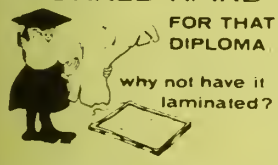

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Clinical Investigation

Low Intracellular Magnesium in Patients With Acute Pancreatitis and Hypocalcemia

ELISABETH RYZEN, MD, *and* ROBERT K. RUDE, MD, *Los Angeles*

To determine the role of magnesium deficiency in the pathogenesis of hypocalcemia in acute pancreatitis, we measured magnesium levels in serum and in peripheral blood mononuclear cells in 29 patients with acute pancreatitis, 14 of whom had hypocalcemia and 15 of whom had normal calcium levels. Only six patients had overt hypomagnesemia (serum magnesium < 0.70 mmol per liter [1.7 mg per dl]). The mean serum magnesium concentration in hypocalcemic patients was not significantly lower than in normocalcemic patients, but the mononuclear cell magnesium content in hypocalcemic patients with pancreatitis was significantly lower than in normocalcemic patients with pancreatitis (P<.01). The serum magnesium level did not correlate with that of serum calcium or the mononuclear cell magnesium content, but the latter did significantly correlate with the serum calcium concentration (r=.81, P<.001). Most patients with hypocalcemia had a low intracellular magnesium content. Three normomagnesemic, hypocalcemic patients with alcoholic pancreatitis also underwent low-dose parenteral magnesium tolerance testing and showed increased retention of the magnesium load. We conclude that patients with acute pancreatitis and hypocalcemia commonly have magnesium deficiency despite normal serum magnesium concentrations. Magnesium deficiency may play a significant role in the pathogenesis of hypocalcemia in patients with acute pancreatitis.

(Ryzen E, Rude RK: Low intracellular magnesium in patients with acute pancreatitis and hypocalcemia. West J Med 1990 Feb; 152:145-148)

Hypocalcemia has been reported to occur in 10% to 80% of patients with acute pancreatitis and is considered a poor prognostic sign.[1-9] The origin of hypocalcemia in acute pancreatitis remains unclear. Magnesium (Mg) deficiency is a known cause of hypocalcemia,[10-15] and patients with acute pancreatitis often have risk factors for magnesium deficiency such as alcohol abuse or diabetes mellitus.[16-18] The role of Mg deficiency in the pathogenesis of hypocalcemia in patients with pancreatitis has been largely unexplored, however. Although a few studies have reported hypomagnesemia in some patients with acute pancreatitis,[2,3,7,8] serum Mg concentrations are usually normal. Magnesium is primarily an intracellular cation, however, and thus serum Mg concentrations may not adequately reflect tissue Mg stores.[16] Low intracellular Mg content is not an uncommon finding in patients with normal serum Mg concentrations.[15-20] We have reported hypocalcemia in normomagnesemic patients with low mononuclear cell Mg, where the hypocalcemia resolved with magnesium therapy.[15] Magnesium deficiency in normomagnesemic patients can also be shown indirectly by a finding of increased retention of a parenterally administered magnesium load.[17-21] In this study, we sought to determine if patients with acute pancreatitis and hypocalcemia have depleted tissue Mg stores that may play a role in the pathogenesis of the hypocalcemia.

Study Design

Patients

We studied 29 patients admitted to the general internal medicine service of the Los Angeles County-University of Southern California Medical Center with the diagnosis of acute pancreatitis. Informed consent was obtained. Patients with an admission clinical diagnosis of acute pancreatitis were selected within 4 to 24 hours of admission based on their availability to have blood drawn on the days that were chosen for study by the investigators. Patients with serum creatinine concentrations of greater than 132.6 μmol per liter (1.5 mg per dl), intensive care unit patients, hemodynamically unstable patients, and patients who had already received magnesium therapy were excluded. In 19 patients pancreatitis had developed as a result of alcohol abuse, and 10 had pancreatitis due to biliary tract disease. Two of the patients with biliary tract disease also had diabetes mellitus. No patient had pancreatic ascites. Of the 29 patients, 14 had hypocalcemia and 15 had normocalcemia (hypocalcemia was defined as a corrected serum calcium concentration of less than 2.12 mmol per liter [8.5 mg per dl]; serum calcium was corrected 0.2 mmol per liter (0.8 mg per dl) for every 1 gram per dl deviation of serum albumin from the mean normal serum albumin level of 40 grams per liter [4 grams per dl]).

From the Department of Medicine, Los Angeles County-University of Southern California Medical Center, and the Orthopedic Hospital Bone and Connective Tissue Research Laboratory, Los Angeles.

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Reprint requests to Elisabeth Ryzen, MD, Department of Medicine, Rm 7900, 1200 N State St, Los Angeles, CA 90033.

ABBREVIATIONS USED IN TEXT

cyclic AMP = adenosine 3′:5′-cyclic phosphate
Mg = magnesium
PTH = parathyroid hormone

Protocol

Fasting morning blood specimens were drawn on all patients to measure serum Mg, calcium, albumin, creatinine, and mononuclear cell Mg content. To further assess for the presence of magnesium deficiency, three normomagnesemic, hypocalcemic patients who agreed to further study after informed consent was obtained underwent low-dose parenteral Mg tolerance testing at the Clinical Research Center, as previously described.[15,21] The percentage of Mg retained was calculated using the following formula:

$$\%\ \text{Mg retained} = \left[1 - \frac{\text{Postinfusion urine Mg} - (\text{preinfusion urine Mg/Cr} \times \text{postinfusion urine Cr})}{\text{total elemental Mg infused}}\right] \times 100,$$

in which Cr is the creatinine concentration.

After our initial assessment of the patients on admission, no further interventions were made in their care, and the patients were managed by their primary physicians as they judged to be appropriate.

Methods

Serum and urine magnesium levels were measured by atomic absorption spectrophotometry. Serum calcium, creatinine, and albumin concentrations were measured by an AutoAnalyzer. Mononuclear cell Mg content was measured using methods previously described.[15,22]

Statistics

Biostatistical analysis was provided by the University of Southern California Clinfo Vax computer. The Wilcoxon nonpaired ranked sum test was used to compare the differences between groups, as the data were not normally distributed.

Results

Table 1 shows the serum magnesium, serum calcium, and mononuclear cell Mg content in the hypocalcemic patients and the normocalcemic patients on admission evaluation.

The mean serum Mg concentration in hypocalcemic patients was not significantly lower than in normocalcemic patients. Only 6 of the 29 patients studied (2 hypocalcemic and 4 normocalcemic) had low (<0.70 mmol per liter [1.7 mg per dl]) serum Mg concentrations. Serum Mg levels did not significantly correlate with serum calcium concentration.

The intracellular Mg content was lower than in normal laboratory controls in most patients in both the hypocalcemic and normocalcemic groups (Figure 1). In addition, the mononuclear cell Mg content was significantly lower in hypocalcemic patients than in normocalcemic patients (0.89 ± 0.05 and 1.08 ± 0.03 μg magnesium per mg protein, respectively, $P < .01$), and the mononuclear cell Mg content correlated with the serum calcium concentration ($r = .81$, $P < .001$). Of note is that 14 of the 15 hypocalcemic patients (93%) had a low intracellular magnesium content (Figure 1). The one who did not had pancreatitis due to biliary tract disease and no known risk factors for magnesium deficiency. Patients with alcoholic pancreatitis had a significantly lower mononuclear cell Mg content than patients with biliary pancreatitis (0.94 ± 0.03 and 1.07 ± 0.07 μg magnesium per mg protein, respectively [$P < .05$]).

TABLE 1.—*Serum Magnesium (Mg), Serum Calcium, and Mononuclear Cell Mg Content in Hypocalcemic and Normocalcemic Patients With Acute Pancreatitis*

Patient Characteristic	Serum Mg, mmol/liter (mg/dl)	Mononuclear Cell Mg, μg/mg protein	Serum Calcium, mmol/liter (mg/dl)
Hypocalcemic, n=14	0.74±0.02 (1.81±0.06)*	0.89±0.05†	1.94±0.03 (7.76±0.12)†
Normocalcemic, n=15	0.76±0.04 (1.85±0.09)	1.08±0.03	2.23±0.01 (8.92±0.06)
Normal range	0.70–0.86 (1.7-2.1)	1.11-1.35‡	2.12-2.57 (8.5-10.3)

*Mean ± standard error of the mean.
†$P < .01$ compared with normocalcemic patients.
‡Normal laboratory controls (Ryzen et al[15] and Ryzen et al[20]).

Table 2 shows the data on the three hypocalcemic, normomagnesemic patients who underwent parenteral magnesium tolerance testing. Retention of the magnesium load given was elevated in all three patients.

We attempted to evaluate the hospital course of the hypocalcemic patients we studied on admission. Unfortunately, more than half were lost to follow-up before their hypocalcemia resolved—two signed out of the hospital against medical advice, two were transferred to another facility, and four were discharged before the hypocalcemia resolved. Of the remaining six hypocalcemic patients, some received magnesium supplements from their primary physicians and some did not; some began eating early in the course of their hos-

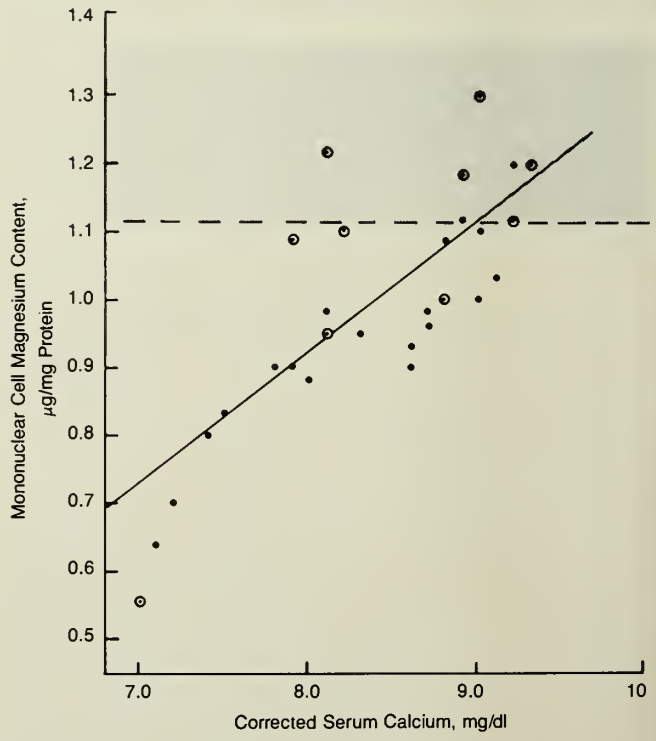

Figure 1.—The graph shows a correlation of serum calcium concentration (in milligrams per deciliter) with mononuclear cell magnesium content (micrograms per milligram of protein; $r = .81$, $P < .001$). The filled circles indicate patients with alcoholic pancreatitis, and the open circles with dots are patients with biliary pancreatitis. The shaded area represents the normal range for mononuclear cell magnesium content (mean ± standard deviation).

TABLE 2.—*Patients Who Underwent Parenteral Magnesium (Mg) Tolerance Testing*

Patient	Serum Mg, mmol/liter (mg/dl)	Serum Calcium, mmol/liter (mg/dl)	Mononuclear Cell Mg, µg/mg protein	Retention at 24 h, %
1	0.74 (1.8)	1.77 (7.1)	0.64	66
2	0.78 (1.9)	1.85 (7.4)	0.80	55
3	0.78 (1.9)	2.02 (8.1)	0.98	45
Normal range	0.70-0.86 (1.7-2.1)	2.12-2.57 (8.5-10.3)	1.11-1.35*	<25†

*Normal laboratory controls (Ryzen et al[15] and Ryzen et al[20]).
†Normal subjects (Ryzen et al[21]).

pital stay, and others remained fasting for prolonged periods of time; some received vigorous intravenous hydration and some did not. No patient died. Although hypocalcemia eventually resolved in all six patients, the number of patients in each subgroup was too small for meaningful statistical analyses.

Discussion

In a number of studies an attempt has been made to elucidate the cause of the hypocalcemia that is seen in patients with acute pancreatitis.[1-8,23-26] Hypoalbuminemia accounts for the presence of hypocalcemia in some but not all patients.[4] Renal failure may be responsible for hypocalcemia in a minority of patients with acute pancreatitis.[8] Edmondson and co-workers originally proposed that hypocalcemia in pancreatitis occurs as a result of saponification of calcium in and around the necrotic pancreas.[3] Although this explanation may apply to a few patients such as those with massive pancreatic ascites,[26] the prolonged duration and intensity of hypocalcemia in patients without ascites suggest a primary disturbance in calcium metabolism. Glucagon release from the inflamed pancreas with the subsequent stimulation of calcitonin secretion has been proposed as a mechanism to explain the hypocalcemia, but glucagon and calcitonin concentrations have not been consistently elevated in such patients.[24,25] Shifts of calcium from extracellular to intracellular spaces have also been reported in experimental pancreatitis in animals.[27]

Impaired parathyroid hormone (PTH) function or PTH end-organ resistance, or both, may contribute to hypocalcemia in acute pancreatitis. Immunoreactive PTH concentrations in acute pancreatitis are variable; some patients have low PTH concentrations or concentrations of PTH that are inappropriately low for the degree of hypocalcemia, and others show elevated PTH concentrations with impaired generation of adenosine 3′:5′-cyclic phosphate (cyclic AMP).[1,2,5-7] End-organ resistance to PTH action has been hypothesized to be due to the hypovolemia that patients with pancreatitis usually manifest, whereby impaired perfusion of bone may result in bony infarcts and impaired mobilization of calcium from bone. Indeed, hypocalcemia is less likely to occur when hypovolemia is absent.[1,23]

Alternatively, magnesium deficiency is a known cause of both impaired PTH release and end-organ resistance to PTH,[10-14] but the role of magnesium deficiency in the pathogenesis of the hypocalcemia of pancreatitis is unclear. Overt hypomagnesemia has been reported in about 25% of patients with pancreatitis,[8] similar to what we found in this study, where 21% of patients had hypomagnesemia. In one study, hypocalcemia was found to be more common and more profound in patients with pancreatitis who had hypomagnesemia; a significant correlation between serum calcium and serum magnesium levels was also noted.[8] We did not find a correlation between serum calcium and serum magnesium levels in this study, but we did find a significant correlation between serum calcium levels and intracellular Mg content (Figure 1). Our study is the first report of depleted intracellular Mg content in hypocalcemic patients with acute pancreatitis. All but one of our hypocalcemic patients with pancreatitis had a low intracellular Mg content. The finding of increased retention of a parenterally administered magnesium load in the three hypocalcemic, normomagnesemic patients with low mononuclear cell Mg content who were studied provides additional evidence for Mg deficiency. Subjects who are not Mg deficient would be expected to retain less than 25% of the magnesium load given.[21]

Further evidence suggesting a possible role of magnesium deficiency in the pathogenesis of the hypocalcemia of pancreatitis is the finding that hypocalcemia is more common and persists longer in patients with alcoholic pancreatitis than in those with pancreatitis of other causes.[28] Our finding that serum calcium was lower in patients with alcoholic pancreatitis than in those with biliary pancreatitis thus supports the hypothesis that magnesium deficiency predisposes patients with acute pancreatitis to the development of hypocalcemia. It is well known that persons with alcoholism are commonly Mg deficient even if serum Mg concentrations are normal.[15-21] Patients with acute pancreatitis are usually dehydrated, and dehydration can result in falsely normal or even increased serum Mg concentrations despite depleted intracellular Mg stores.[19] It is thus not surprising that only a few patients with pancreatitis were hypomagnesemic, but most had depleted intracellular Mg. These cellular Mg deficits may have predisposed some patients to the development of hypocalcemia. Of interest was the finding that the only patient with hypocalcemia who did not have depressed intracellular Mg content was a patient with pancreatitis of a biliary cause (Figure 1). This patient also had no other risk factors for magnesium deficiency. In this patient, factors other than a low tissue Mg content were probably responsible for the hypocalcemia. The two other patients with biliary pancreatitis who did have low mononuclear cell Mg content were diabetic, and diabetes mellitus is another known risk factor for magnesium deficiency.[16]

Not all patients with low intracellular Mg were hypocalcemic. Malregulation of the adenylate cyclase-cyclic AMP system in the parathyroid glands and PTH end organs is thought to be the cause of the hypocalcemia of magnesium deficiency.[29] Concentrations of PTH in Mg-deficient patients can be low, normal, or high.[10-14] We did not measure PTH levels or end-organ responsiveness to PTH in our subjects. Previous reports of PTH concentrations in patients with pancreatitis and hypocalcemia have also shown PTH concentrations to be low, normal, or high,[1,7] but the intracellular Mg content was not measured in those patients. In this study we also did not measure ionized calcium concentrations, choosing instead to adjust the total measured serum calcium concentrations for the serum albumin. We deliberately excluded intensive care unit patients, as in such patients the correlation of corrected serum calcium concentrations with ionized serum calcium concentrations is not good.[30] It is still possible, however, that our classification of particular pa-

tients into hypocalcemic and normocalcemic groups might have been different had we measured ionized calcium levels. Thus, perhaps some of the patients with low intracellular Mg content and normal "corrected" serum calcium concentrations might really have low ionized calcium concentrations, and vice versa.

Finally, even though our patients had evidence of intracellular magnesium depletion, it is possible that this was unrelated to their hypocalcemia and that an as-yet-unidentified factor is primarily responsible for the hypocalcemia of acute pancreatitis. Although our data clearly do not prove definitively that the depleted tissue magnesium content was responsible for or even contributed to the hypocalcemia in these patients, our finding that almost all patients with acute pancreatitis and hypocalcemia have depleted intracellular Mg content should be borne in mind when deciding on the proper management of patients with acute pancreatitis and hypocalcemia. Specifically, our data suggest that Mg repletion therapy should be considered even in a normomagnesemic patient with pancreatitis who has hypocalcemia, especially if that person has risk factors for magnesium deficiency such as alcoholism or diabetes mellitus and renal function is normal. Hypocalcemia is considered a poor prognostic sign in patients with acute pancreatitis[9] and is thought to reflect the severity of the disease. What is not clear is if the hypocalcemia itself contributes to the morbidity. Hypocalcemia can contribute to hypotension in critically ill patients[31] and is a poor prognostic sign in critically ill patients in general.[32] Moreover, if hypocalcemia is a reflection of magnesium deficiency, it is thus possible that other clinical manifestations of magnesium deficiency such as cardiac arrhythmias,[33] respiratory muscle weakness,[34] and refractory hypokalemia[35] may contribute to patients' morbidity. Indeed, clinical complications known to be associated with magnesium deficiency such as cardiac arrhythmias[36] and refractory hypokalemia[37] have been seen in patients with normal serum Mg levels but depleted tissue Mg content, with clinical improvement with magnesium therapy. In this study, we unfortunately could not assess adequately the role of Mg deficiency in determining the prognosis, as only patients without severe disease were selected for study, and they received variable therapy by their primary physicians after our initial evaluation of them on admission.

In Mg-deficient hypocalcemia, resistance to calcium and vitamin D supplementation is seen, and Mg supplementation is recommended for optimal management.[16] We have previously reported treatment of normomagnesemic patients with depleted intracellular Mg stores and unexplained hypocalcemia with Mg supplementation, with resolution of the hypocalcemia.[15] We have found that 32 to 64 mEq of elemental Mg as magnesium sulfate can be added to a patient's intravenous fluids each day as a continuous infusion without producing hypermagnesemia, provided renal function is adequate. This can be administered for three to five days to help replete tissue Mg stores and correct hypocalcemia, or at least until the patient is eating normally and not receiving medications such as intravenous saline or aminoglycosides that can result in urinary Mg losses.[16] Magnesium homeostasis and clinical disorders of Mg deficiency are reviewed in detail elsewhere.[16,38]

In summary, we have found depletion of intracellular Mg in most patients with hypocalcemia and pancreatitis. Further studies are needed to determine the clinical significance of this finding and the potential benefits of Mg supplementation in such patients.

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Clinical Medicine

Long-Acting Nifedipine Versus Metoprolol as Monotherapy for Essential Hypertension

A Randomized, Controlled Crossover Study

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We assessed the efficacy of long-acting nifedipine as monotherapy in 52 patients with mild to moderate essential hypertension in a randomized, controlled crossover study. Good blood pressure control was achieved in 34 of 40 patients (85%) receiving nifedipine (mean daily dose, 52 mg in 2 divided doses) compared with 23 of 40 patients (58%) receiving metoprolol (mean daily dose, 155 mg in 2 divided doses). After treatment for 4 weeks, the mean blood pressures with nifedipine (149.7 ± 16.6/88.7 ± 11.1 mm of mercury) and metoprolol administration (163.9 ± 23.3/94.2 ± 10.2 mm of mercury) were significantly lower than with placebo (176.7 ± 17.3/100.9 ± 7.1 mm of mercury) (P < .05). The mean systolic pressure during nifedipine treatment was 14.2 mm of mercury lower (95% confidence interval [CI], 3.9 to 24.5 mm of mercury) and mean diastolic pressure 5.5 mm of mercury (95% CI, 0.3 to 10.7 mm of mercury) lower than with metoprolol therapy. Both drugs were reasonably well tolerated, and intolerance requiring withdrawal was encountered in 3 of 45 (7%) patients receiving nifedipine, compared with 1 of 45 (2%) of those taking metoprolol and placebo, respectively. Adverse effects of nifedipine, most of which were transient, included palpitations, headache, facial flushing, and ankle edema. Long-acting nifedipine is a promising agent when given alone for mild to moderate hypertension and can be safely administered in clinical practice.

(Woo KS, Pun CO: Long-acting nifedipine versus metoprolol as monotherapy for essential hypertension—A randomized, controlled crossover study. West J Med 1990 Feb; 152:149-152)

For the past two decades, diuretics and β-blockers have been commonly used as first-line drugs in treating hypertension.[1-3] Some large-scale long-term studies, however, have revealed certain side effects of the diuretics and β-blockers and shown that they are not well tolerated in certain patients.[4-7] These observations have stimulated interest in alternative drug regimens. Calcium antagonists have been found safe and effective in treating hypertensive crises and resistant hypertension, although experience using them as first-step monotherapy for hypertension is still limited.[8-10] With the availability of a slow-releasing and more convenient long-acting preparation of nifedipine, its use as a first-line drug for treating mild to moderate hypertension is theoretically appealing.[11,12]

In this article we report our experience with such a slow-releasing, long-acting preparation, nifedipine retard, as monotherapy for essential hypertension as compared with an established β-blocker, metoprolol.

Patients and Methods

After explaining the nature of the study and obtaining informed consent, we recruited 52 patients with mild to moderate essential hypertension seen in the hypertension clinic at the Prince of Wales Hospital (Hong Kong) between September 1985 and April 1987. Inclusion criteria were mild to moderate hypertension with a blood pressure of 160/95 to 219/114 mm of mercury for at least three readings on two separate occasions; age younger than 70 years; an absence of complications of hypertension, including myocardial infarction, renal impairment, heart failure, or cerebrovascular accident, and of other major systemic disease; and essential hypertension.

Patients with underlying causes, severe hypertension (blood pressure ≥220/115 mm of mercury), or contraindications for β-blockers were excluded from the study. Women included in the study were neither pregnant nor lactating.

During each visit, the blood pressure was measured at the same time of the day (10 AM to 12 noon) and at 12 hours after the last dose of pills. The same research nurse took all blood pressure measurements using a random-zero sphygmomanometer with the patient in the sitting position after five minutes of rest and after standing for two minutes. Korotkoff phase 5 was taken as the diastolic pressure, and the average of three readings was recorded in each posture.

After a run-in period of four weeks when no active treatment was given, patients were randomly divided into two

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The United College of the Chinese University of Hong Kong sponsored a research student in this study under the Student Campus Work Scheme. Nifedipine retard and placebo tablets and personal computer service were provided by the Bayer China Company, Limited (Hong Kong).

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TABLE 1.—*Blood Pressure (BP; mm of mercury) in Different Periods of Nifedipine, Metoprolol, and Placebo Treatment*

Patient Group and BP	First Phase: Placebo, Weeks 1-4	First Phase: Drug, Weeks 5-8	Second Phase: Placebo, Weeks 9-10	Second Phase: Drug, Weeks 11-14
Group A*				
Systolic	175.8±22.8	166.3±24.1†	177.4±32.7	149.8±19.1‡
Diastolic	101.8± 8.1	93.7± 7.8§	100.6±12.0	86.9±10.4‖
Group B¶				
Systolic	178.3±18.0	149.5±14.1†	170.9±23.7	161.6±22.8‡
Diastolic	101.6± 8.1	90.6±11.7§	98.5±10.3	94.7±12.3‖
P Value#	>.5		>.1	

*Metoprolol therapy, then nifedipine therapy.
†$P<.01$
‡$P<.05$
§$P>.1$
‖$P<.02$
¶Nifedipine therapy, then metoprolol therapy.
#Group A versus group B.

groups. Group A received titrated doses of 50 to 100 mg of metoprolol twice a day, and group B received 20 to 40 mg of nifedipine retard twice a day for four weeks to return the blood pressure to a normal range of 130/70 to 160/90 mm of mercury. A washout period of two weeks followed, after which patients were crossed over to the other drug, that is, nifedipine retard was administered to group A and metoprolol to group B for another four weeks. Patients were given a placebo tablet twice a day during the run-in and washout periods. So that their blood pressure response could be assessed during stress, patients were given a submaximal treadmill exercise test for eight to nine minutes using the Bruce protocol up to stage 3 on completion of the study while they were maintained on a regimen of one of the two drugs.

An electrocardiogram, chest x-ray film, and hematologic and biochemical profiles were carried out during each treatment period. At each visit an adverse effects questionnaire was administered, and any adverse symptoms were recorded in detail.

Six patients whose blood pressures returned to normal and one with a pressure of 220/115 mm of mercury or more during the second washout period were removed from the study. Five other patients requiring withdrawal because of adverse symptoms were excluded from the analysis of blood pressure responses, but they were included in the analysis of adverse side effects.

Paired t and χ^2 tests were used to assess the statistical significance of differences in blood pressure readings and adverse reactions.[13] Blood pressure results are given as the mean ± 1 standard deviation. The 95% confidence intervals (CI) for the difference in blood pressure readings were calculated.[14]

Results

Patients' ages ranged from 32 to 70 years with a mean of 54.3 ± 11.9 years. Of the 40 patients completing the two phases of study, 19 were men; 28 (70%) patients received 40 mg of long-acting nifedipine, 12 (30%) were given 80 mg of long-acting nifedipine, 18 (45%) received 100 mg of metoprolol, and 22 (55%) received 200 mg of metoprolol daily, all in two divided doses. Blood pressure levels are shown in Table 1. Good blood pressure control was achieved in 85% of patients receiving nifedipine, a mean daily dose of 52 mg in two divided doses, compared with 58% of patients taking metoprolol, a mean daily dose of 155 mg in two divided doses (Table 2). The mean sitting systolic blood pressure of patients taking nifedipine was 14.2 mm of mercury (95% CI, 3.9 to 24.5 mm of mercury) and the mean diastolic blood pressure was 5.5 mm of mercury (95% CI, 0.3 to 10.7 mm of mercury) lower than those of patients receiving metoprolol (Table 2, Figure 1). During treadmill exercise, the mean maximal blood pressure was similar with both drugs. No significant effect of the body posture on the blood pressure was seen with either drug, but the standing heart rates were slightly higher in the nifedipine and placebo periods than in the metoprolol period (Figure 2). Heart rates were lowest while patients received metoprolol ($P<.001$).

Of 45 patients, adverse symptoms were reported in 13 (29%) taking nifedipine compared with 7 (16%) receiving metoprolol ($P>.05$), 35% receiving placebo run-in, and 31% of patients on placebo washout ($P>.5$) (Table 3). These symptoms included facial flushing (4% nifedipine, 2% placebo) and ankle edema not associated with a significant increase in body weight (9% nifedipine). Headache was a common complaint, being present in 19% of patients receiving placebo, 4% of patients taking metoprolol, and 24% of those taking nifedipine. Some patients experienced dizziness (13% nifedipine, 11% to 15% placebo, 7% meto-

TABLE 2.—*Blood Pressure (BP; mm of mercury) Control With Nifedipine Therapy Versus Metoprolol Therapy**

Blood Pressure Indices	Patients: Metoprolol, Mean Dose 155 mg/d, No.	(%)	Patients: Nifedipine, Mean Dose 52 mg/d, No.	(%)
Excellent (≤140/80)	13	(32)	20	(50)
Good (140/80 to 155/90)	10	(25)	14	(35)
Overall	23	(58)	34	(85)
Mean systolic	163.9±23.3		149.7±16.6	
Difference (95% CI)	14.2 (3.9-24.5)†			
Mean diastolic	94.2±10.2		88.7±11.1	
Difference (95% CI)	5.5 (0.3-10.7)‡			
Baseline BP (at rest)§				
Mean maximum systolic	161.3±26.4		163.4±21.0	
Mean maximum diastolic	90.0±13.1		88.2± 7.2	
During exercise§				
Mean maximum systolic	189.3±17.9		192.5±18.8	
Mean maximum diastolic	93.7±13.4		94.2± 8.2	

CI=confidence interval

*Mean values are given as mean ± 1 SD.
†$P<.01$.
‡$P<.05$.
§$P>.1$ (nifedipine versus metoprolol).

prolol), tiredness (11% metoprolol, 4% nifedipine, 2% to 6% placebo), and palpitations (7% nifedipine, 2% to 4% placebo). Most symptoms were of minor inconvenience only. Withdrawal of drugs was required on five occasions, once each for palpitations, facial flushing, and headache during nifedipine therapy (three women); in one man because of headache during treatment with placebo; and in another man because of tiredness while receiving metoprolol. There were no notable changes in cardiac size, renal function, or other biochemical indices, including cholesterol and random glucose levels, during treatment with either drug (Table 4).

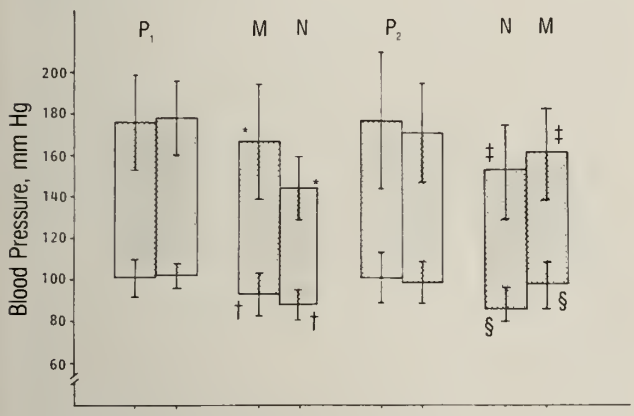

Figure 1.—The graphs show blood pressures during placebo run-in (P_1), placebo washout (P_2), metoprolol (M), and nifedipine (N) periods. * = $P<.01$, † = $P>.1$, ‡ = $P<.05$, § = $P<.02$

TABLE 3.—*Patients Having Side Effects in Different Periods of Nifedipine, Metoprolol, and Placebo Treatment*

Side Effect	Placebo Run-in No. (%)	Placebo Washout No. (%)	Metoprolol No. (%)	Nifedipine No. (%)
Gastrointestinal upset	3 (6)	0 (0)	4 (9)	3 (7)
Flushing	1 (2)	0 (0)	0 (0)	2 (4)*
Edema	0 (0)	0 (0)	0 (0)	4 (9)
Headache	10 (19)	8 (18)*	2 (4)	11 (24)*
Dizziness	8 (15)	3 (7)	3 (7)	6 (13)
Tiredness	3 (6)	1 (2)	5 (11)*	2 (4)
Palpitations	2 (4)	1 (2)	1 (2)	3 (7)*
Other	11 (21)	5 (11)	8 (18)	14 (31)
Withdrawal from study	0 (0)	1 (2)	1 (2)	3 (7)
None	34 (65)	31 (69)	38 (84)	32 (71)
Total count	52	45	45	45

*One patient withdrew because of adverse effects.

Discussion

In our study we were able to objectively evaluate the efficacy and safety of a new long-acting, slow-releasing preparation of nifedipine in patients with mild to moderate essential hypertension. Blood pressure was measured objectively with a random zero sphygmomanometer; thus, any digit preference or observer bias of either tested drug was minimized. To ensure a fair comparison of the potencies of these two drugs, only 40 patients who completed both phases of therapy were included, and 7 patients whose blood pressures remained normal or too high during the second placebo washout period were excluded. Of the latter patients, three had metoprolol and four had nifedipine as their first active drug, and their exclusion probably did not distort or affect the overall evaluation.

This study shows that the long-acting preparation of nifedipine is an effective antihypertensive drug and perhaps more potent than the commonly used β-blocker, metoprolol.[15,16] When nifedipine was used as monotherapy, blood pressures returned to normal in 85% of patients with mild to moderate essential hypertension compared with 58% of patients taking metoprolol alone. This range of potency compares favorably with that of many other antihypertensive agents and is similar to that reported with the use of alternative calcium channel blockers such as verapamil and diltiazem.[10,17,18] The response rate to metoprolol therapy (58%) is similar to that reported from many studies in western countries.[15,16]

Adverse effects were often transient, and most were rea-

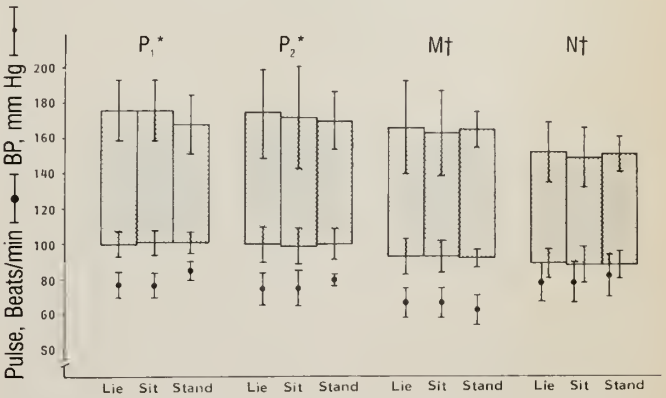

Figure 2.—The graphs show blood pressures and pulse rates in different postures. The P values in different periods refer to comparisons between the corresponding systolic and diastolic blood pressures in different postures. * = $P>.05$, † = $P>.1$

TABLE 4.—*Biochemical and Radiologic Profiles of Patients Receiving Placebo, Metoprolol, and Nifedipine (Mean ± 1 SD)**

Laboratory and X-Ray Variable	Placebo Run-in	Placebo Washout	Metoprolol	Nifedipine
Potassium, mmol/liter	3.9 ± 0.4	4.0 ± 0.5	4.1 ± 0.5	3.7 ± 0.3
Calcium, mmol/liter	2.4 ± 0.1	2.4 ± 0.9	2.3 ± 0.1	2.3 ± 0.1
Urea nitrogen, mmol/liter	5.9 ± 1.4	6.3 ± 1.5	6.3 ± 1.5	6.3 ± 1.5
Creatinine, μmol/liter	81.0 ±21.7	81.7 ±13.5	81.7 ±16.7	78.6 ±20.4
Urate, mmol/liter	0.37± 0.09	0.39± 0.08	0.39± 0.08	0.37± 0.07
Glucose, mmol/liter	5.2 ± 1.3	5.2 ± 1.0	5.1 ± 1.1	5.1 ± 1.0
Cholesterol, mmol/liter	5.9 ± 1.0	5.5 ± 1.3	5.1 ± 1.3	5.5 ± 1.1
Chest x-ray†	51.0 ± 3.9	51.8 ± 1.6	52.5 ± 3.7	49.2 ± 3.4

*Metoprolol or nifedipine versus placebo, $P>.1$.
†The numbers represent the cardiothoracic ratio.

sonably well tolerated. The side-effect profile of this slow-releasing preparation appears to be better than that reported with plain nifedipine preparations.[19] A number of untoward reactions, as revealed by answers to the questionnaire, were also present during the two placebo periods, illustrating the justification and importance of including such control periods in any critical evaluation. Some of these adverse effects, such as headache and dizziness, could be related to high blood pressure. Specific adverse reactions to nifedipine included facial flushing and headache, which have also been reported with the use of other calcium channel blockers and presumably are related to excessive vasodilation in sensitive subjects.[10,20] The exact mechanism of ankle edema is still not well defined. It was not associated with an increase in body weight and is therefore unlikely to be related to pseudotolerance with fluid retention. Its presence usually requires nothing more than reassuring patients of its benign nature. Although we saw no significant changes in heart rates with the use of nifedipine as compared with placebo, three patients (7%) experienced palpitations, presumably due to reflex tachycardia, and withdrawal of one patient was required. Previous studies have reported either no change or a mild increase in heart rates, the differences perhaps being explained by patient selection or study design.[21,22] Freedom from cardiac slowing with the use of nifedipine may have appeal in the setting of bradyarrhythmias, conduction disorders, or when combination therapy with β-blockers is being contemplated. No postural change in blood pressure or any adverse biochemical changes were encountered, and tachyphylaxis was not seen. Gastrointestinal upset such as constipation and cardiac-slowing effect have been reported with the use of verapamil and diltiazem, but, on the whole, their acceptance rates are similar.[17,20]

A twice-a-day regimen of long-acting nifedipine is more convenient than the plain capsule taken three or four times a day, and patients' compliance is likely to be greater with this regimen. Nifedipine is relatively more expensive, however, than other common step-one medications, which could limit its wider use as initial monotherapy in many developing countries with limited financial resources. A greater therapeutic prospect for calcium antagonists as step-one therapy may be the presence of coexisting diseases including ischemic heart disease, chronic obstructive airway disease, or peripheral vascular disease, where beneficial actions on vascular or bronchial smooth muscles are particularly appealing.[23-25] Some preliminary reports have suggested a vascular protective effect by nifedipine in vitro and in animal models, which, if confirmed in humans, could be an additional bonus of this group of drugs in the treatment of hypertension.[26] The implications of such therapy in the primary prevention of coronary artery disease and general atherosclerosis in hypertensive patients is certainly exciting but remains to be proved.

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Clinical Review

Mohs' Micrographic Surgery of the Head and Neck

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Mohs' micrographic surgery, a method originally developed in the 1930s to remove contiguously spreading cutaneous cancers under precise microscopic control, has emerged as the most reliable method for removing certain primary, incompletely excised, and recurrent basal cell and squamous cell carcinomas. Indications for its use have expanded to include many other cutaneous and noncutaneous neoplasms. Usually done as an outpatient procedure and using local anesthesia, a layer of tissue is excised, mapped in relation to the site of removal, sectioned horizontally, and examined for the presence of residual tumor. This sequence is repeated, removing only tissue that contains residual tumor, until a margin completely free of cancer is reached. Extremely high cure rates are achieved, and surrounding tissue is maximally conserved for wound repair.

(Darmstadt GL, Steinman HK: Mohs' micrographic surgery of the head and neck. West J Med 1990 Feb; 152:153-158)

Skin cancer is the most common carcinoma in humans, with an annual incidence of more than 500,000 cases.[1] The most common types are the nonmelanoma carcinomas: basal cell carcinoma and, less frequently, squamous cell carcinoma. About 85% of these cutaneous neoplasms present on the head or neck. The majority are of extremely low metastatic potential, have well-defined borders, and are treated by excision, electrosurgery, cryosurgery, or irradiation with greater than 90% overall success (Table 1).[2] For treatment of the other, more difficult primary, recurrent, and incompletely excised skin carcinomas, Mohs' micrographic surgery gives the most reliable assurance of tumor-free margins regardless of tumor shape, size, depth, or invasion into bone or cartilage or along nerves or blood vessels. This procedure also conserves the maximum amount of normal tissue.

Historical Development

As a medical student in the mid-1930s, Frederick Mohs, MD, developed a method for removing cutaneous cancers under complete microscopic control. He began by examining the leukocytic reaction in normal and cancerous tissues of rats following the administration of various irritants and noted that a 20% solution of zinc chloride produced tissue fixation rather than just irritation. On removing the fixed tissue, he noted excellent preservation of its microscopic features.[3] He then conceived the idea of applying zinc chloride to various carcinomas, fixing them in situ, removing the cancer in layers, and microscopically examining each layer until a tumor-free plane was reached.[4] In the 1940s and 1950s there was much reluctance to accept Mohs' technique. The zinc chloride fixative seemed old-fashioned, bordering on quackery, and many surgeons were contemptuous of deliberately incising through known cancer and removing tissue piecemeal. But as Mohs produced high cure rates, preserved maximal amounts of adjacent normal tissue, and frequently salvaged patients who had been deemed inoperable, the value of the method began to be recognized.

In 1953 Mohs introduced a modification, the fresh-tissue technique, using a local anesthetic and no fixative, for cancer of the eyelid margins, where swelling and discomfort due to zinc chloride treatment was particularly troublesome.[5] In 1974 Tromovitch and Stegman provided significant impetus to the more widespread use of the fresh-tissue technique when they presented results from the first series of patients on whom this technique was used.[6] For the treatment of difficult basal cell carcinomas, this study showed a success rate similar to that with the fixed-tissue technique. Also, by omitting the zinc chloride treatment, several advantages were noted: the perioperative pain from tissue fixation in situ was relieved; several stages could be done in one day, allowing complete treatment in a few hours; and the tissue slough that occurred after the final stage of chemical fixation was eliminated, permitting immediate reconstruction of the surgical wound when indicated. Because of its many advantages, the fresh-tissue technique has replaced the fixed-tissue one, and most surgeons doing Mohs' technique now use the fresh-tissue technique exclusively.

Braun outlined some situations where the fixed-tissue method may still be advantageous[7]:

- Basal cell carcinomas invading bone, meninges, or brain;
- Squamous cell carcinomas invading deeply and around narrow spaces such as the external auditory canal;
- Lesions on highly vascular structures such as the penis; and
- Miscellaneous situations for the palliative removal of large, unresectable neoplasms.

Mohs also advocated using the fixed-tissue technique for malignant melanoma.[8] With the exception of melanoma, how-

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TABLE 1.—*Comparative Success in Treatment Methods Used for Basal Cell Carcinoma**

Treatment Method	Success Rate, %	Treatment Method	Success Rate, %
Electrosurgery	92.6-98.0	Radiation therapy	92.1-96.0
Excisional surgery	93.2-95.5	Mohs' surgery	97.4-99.1
Cryosurgery	94.0-97.0		

*From Swanson et al.[2]

ever, most surgeons using microscopic control think that even these cases can be handled with the fresh-tissue technique. Current research on melanoma will help clarify the role of Mohs' micrographic surgery in treating these tumors.

There are many synonyms for the technique, including chemosurgery and fixed-tissue technique, chemosurgery and fresh-tissue technique, microscopically controlled surgery, microcontrolled surgery, Mohs' microscopic surgery, Mohs' histographic surgery, Mohs' technique, Mohs' surgery, and the acronym MOHS (microscopically oriented histographic surgery). The nomenclature recommended by the American College of Mohs' Micrographic Surgery and Cutaneous Oncology is "Mohs' micrographic surgery."[9]

Surgical Technique

A surgeon begins by outlining the visible clinical margins of the lesion. After the induction of local anesthesia, the tumor is debulked with a scalpel or curette. Then, with the scalpel angled at approximately 45 degrees to the skin to create a beveling effect, a thin layer of tissue is removed 2 to 4 mm beyond the clinical margin of the tumor.

At the time of tissue removal, several steps are taken to ensure the proper orientation of the excised specimen. Before the specimen is completely detached, orientation marks are made on the excised tissue and at corresponding points on the surrounding skin using a scalpel, dyes, sutures, or staples. A map is drawn showing the relative size and shape of the specimen in relation to the area of the body from which it was taken. The tissue is cut on the orientation marks into pieces small enough to fit on a microtome cassette. Each of these smaller specimens is then numbered, turned over so that the undersurface is facing up, and color coded on the cut edges with stains. The position of the numbered specimens and the color coding schema are also indicated on the map.

A technician then carefully cuts from the undersurface serial frozen horizontal sections 5 to 7 μm thick. By first compressing the tissue flat and cutting horizontally across the bottom, the entire edge and undersurface of the excised tissue is sectioned. Horizontal sectioning is pivotal to Mohs' micrographic surgery, as it allows the complete peripheral and deep margins of the removed tissue to be examined. This has been superior to conventional vertical sectioning in showing all contiguous strands of tumor.[10,11] The sections are interpreted by the surgeon with or without the aid of a pathologist, and any remaining tumor foci are precisely located on the map and, therefore, also on the patient. An essential and unique feature of this technique is the active involvement of the surgeon in all phases of the procedure, including the orientation and processing of the surgical specimen, interpreting the histologic slides, and personally marking areas of residual tumor on the Mohs map. The Mohs' micrographic surgeon can then return to the patient and precisely remove only tissue where tumor is microscopically present.

The process can be repeated as often as necessary to extirpate tumor totally, removing only tissue with residual neoplasm and maximally preserving normal surrounding tissue. Because several stages can be completed in a day, and most tumors can be completely removed in three layers or less, all except the most advanced cancers can be removed in one day as an outpatient procedure. When a plane free of cancer is reached, the wound can be allowed to heal by second intention or may be closed primarily.[12,13]

Indications for Mohs' Micrographic Surgery

Mohs' micrographic surgery has become most widely accepted for the treatment of certain basal cell and squamous cell carcinomas. Because the procedure is labor-intensive, time-consuming, and expensive, and because most cutaneous carcinomas are successfully removed by routine methods (Table 1), Mohs' micrographic surgery should be used only for specific indications.

Basal Cell Carcinoma

Overall indications for the use of Mohs' micrographic surgical treatment of basal cell carcinoma include primary tumors in locations associated with an increased risk of local invasion and recurrence such as the midface and ear, tumors larger than 1 to 2 cm, or tumors with aggressive histopathologic or clinical characteristics indicative of a poor treatment response (Table 2). Incompletely excised and recurrent basal cell carcinomas are also generally best approached with the Mohs technique.

Primary basal cell carcinoma. Tumor location: Some

TABLE 2.—*Indications for Mohs' Micrographic Surgery*

- Basal cell carcinoma
  - Primary
    - Problem anatomic location, nose, eyes, ears, and embryonic fusion planes
      - High propensity for recurrence
      - Cosmetic or functional import or both
    - Aggressive histopathologic features
      - Morpheaform or sclerosing
      - Infiltrating
      - Metatypical
    - Size >2 cm diameter
    - Indistinct clinical margins
  - Incompletely excised
  - Recurrent
- Squamous cell carcinoma
  - Primary—same principles as above for basal cell carcinoma
  - Incompletely excised
  - Recurrent
  - Radiation-induced
  - Bowen's disease (gluteal cleft or vulvar)
- Other cutaneous lesions
  - Any locally invasive lesion with histologic features interpretable by frozen section
- Noncutaneous neoplasms (selected cases)
  - Parotid gland
  - Tongue
  - Oral cavity
  - Palate
  - Tonsillar pillars
  - Paranasal sinus

basal cell carcinomas send out silent, contiguous, subclinical extensions along planes of least resistance,[14] including fascial planes, periosteum, perichondrium, blood vessels, nerve sheaths, and the tarsal plate of the eyelid. Another important mode of spread is along embryonic fusion planes,[15] such as the junction of the nasal ala with the nasolabial fold, the preauricular area, especially the tragus, and the postauricular sulcus. Tissue planes at these sites may extend in a direction perpendicular to the surface of the skin, facilitating tumor invasion to unexpected depths.

Carcinomas in the central face tend to be more invasive, more destructive, more often recurrent, and more difficult to treat than similar tumors in other sites. Roenigk and associates analyzed the odds ratios of 239 recurrent basal cell carcinomas treated at the Cleveland Clinic Foundation from 1981 to 1983, providing an estimate of the relative risk of a recurrent basal cell cancer developing in a specific location compared with that of a tumor not in that location—that is, an odds ratio of 1.00 means there is an equal risk of recurrent tumor in a specific location compared with all other anatomic sites. Areas of particularly high risk of recurrence for basal cell carcinoma were concentrated in an H shape in the midfacial, auricular, and periauricular areas (Figure 1). Areas of specific concern are the junction of the ala with the nasolabial fold; the nasal ala; the nasal septum; the periauricular region, extending to the temple; the periorbital region, specifically the lower eyelid and the inner canthus; and certain scalp lesions.[16-19] The skin and subcutaneous tissue of both the midface and the ear are relatively thin and in close proximity to cartilage and bone, allowing the spread of tumor along the perichondrium and periosteum.[19,20] Robins noted that the preauricular area has the highest recurrence rate following Mohs' micrographic operation over any other anatomic site.[21] The ear can be particularly difficult to manage because of tracking of tumor down the external auditory canal, where it can gain access to the mastoid. The postauricular sulcus is an embryonic fusion plane in which tumor often grows in an aggressive manner. In the periorbital region, inner canthal tumors can often extend to and around the ethmoid sinuses; the resulting deep orbital spread of tumor can necessitate enucleation. The aggressive nature of basal cell carcinoma in the scalp is well documented, with occasional deep invasion and extension along the periosteal plane. Once the calvarium is penetrated, tumor can extend to involve the dura.[22]

Cosmetic and functional ramifications are the second reason that tumor location is particularly important. Key areas of cosmetic import include the nasal tip, the nasal ala, the upper lip, the helix, and the eyelids. A maximal preservation of normal tissue in these areas is necessary for proper postsurgical reconstruction.

Tumor histology: Tumors of standard histologic features, such as nodulocystic or adenoid, present little therapeutic challenge and can be handled routinely. Tumors with an aggressive histologic behavior, however, often warrant the more exacting treatment of Mohs' micrographic surgical technique.[16,23] These histologic subgroups include morpheaform or sclerosing basal cell carcinoma, superficial multicentric tumors, or aggressive metatypical basal cell carcinoma—previously referred to as basosquamous or keratinizing basal cell carcinoma. Greater subclinical extension,[24,25] particularly in the preauricular area,[24] and a higher rate of recurrence[19,23,26,27] have been documented with these tumor types, making Mohs' micrographic surgery the most appropriate initial therapeutic approach.

Tumor size: The success rate in treating basal cell carcinoma declines with increasing tumor size, especially when the tumor is larger than 1 to 2 cm.[16,18,21,28-33] Mohs reported a 99.8% cure rate for tumors less than 2 cm, 98.6% for tumors between 2 and 3 cm in size, and 90.5% for tumors greater than 3 cm in diameter[28]; the success rate declines more rapidly with increasing tumor size when routine methods are used. Therefore, basal cell carcinomas larger than 2 cm should be treated aggressively, and Mohs' micrographic operation should be considered.

Clinical characteristics: Most basal cell carcinomas are slow-growing and somewhat nodular in character, with distinct borders. There are subgroups, however, that are more rapidly growing, have ill-defined clinical borders, and are multicentric. These can be more difficult to treat and may be appropriate for Mohs' surgery.

Previous incomplete excision. If tumors with pathologically positive margins are watched clinically with no reexcision, high recurrence rates may result. Thomas found that incompletely excised tumors in the perinasal, periauricular, and periorbital regions recurred 82% of the time; on the rest

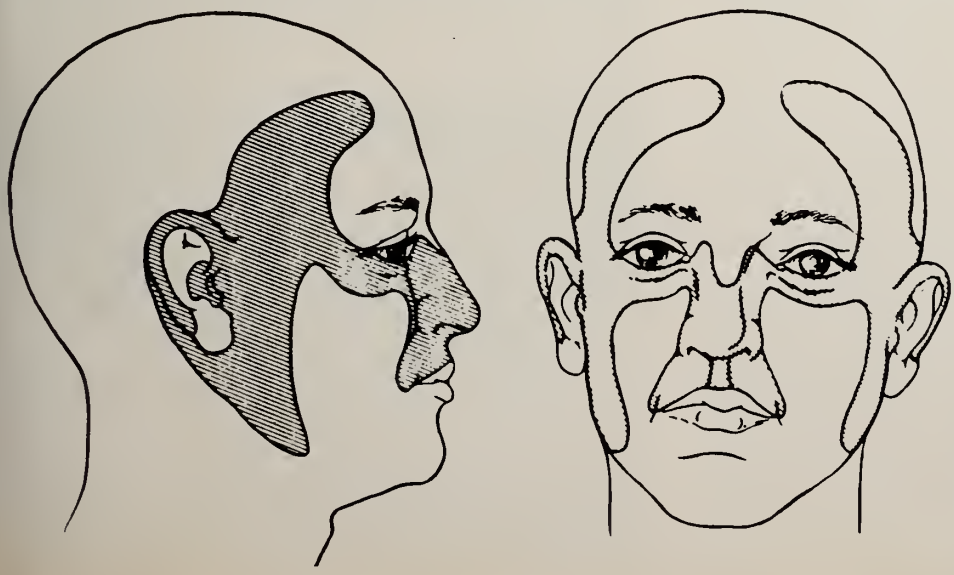

Figure 1.—The tumor location plays an important role in treating basal cell carcinoma. The shaded areas represent anatomic locations on the head and neck that warrant special consideration for Mohs' micrographic surgery (from Swanson et al[2]).

of the head and neck, 25% of incompletely excised tumors recurred.[34] Mohs' micrographic surgery is an excellent follow-up treatment of these inadequately excised tumors that preserves the maximum amount of normal surrounding skin.

Recurrent basal cell carcinoma. A success rate of greater than 96% for treating recurrent basal cell carcinoma by micrographic surgery is well documented,* in contrast to lower success rates, often around 50%, for retreatment of these tumors by conventional means.[10,16,21,28,30,36,37] Therefore, when the Mohs microsurgical technique is available, it should be the treatment of choice for recurrent basal cell carcinomas.

Squamous Cell Carcinoma

Squamous cell and basal cell carcinomas behave and are treated in a similar manner. Routine, small, clinically less aggressive tumors that are actinically derived and are located in anatomic sites of low risk for metastasis or recurrence can be adequately treated using routine methods. As with basal cell carcinoma, however, those squamous cell carcinomas that occur in difficult anatomic sites, are large, or have an aggressive clinical nature are best handled using Mohs' techniques. Incompletely excised and recurrent tumors should also be treated using these techniques. Additional selected types and locations of squamous cell carcinoma can best be approached by Mohs' micrographic surgery, including tumors on previously irradiated skin[2] and Bowen's disease of the gluteal cleft or vulva.[13] Keratoacanthoma, although not a true squamous cell carcinoma, can grow in an aggressive manner in the central facial area; some advocate that these be treated like a squamous cell carcinoma, and, accordingly, many are manageable by Mohs' extirpation.[13]

Additional Applications of Mohs' Surgery

In general, any contiguously growing tumor that invades locally, recurs locally, and has histologic features amenable to frozen section interpretation can be treated using Mohs' surgery. Those that have been treated successfully using this technique include verrucous carcinoma, angioendothelioma, dermatofibrosarcoma protuberans, malignant fibrohistiocytoma, leiomyosarcoma, primary adenocystic carcinoma of the skin, primary Merkel cell carcinoma, meibomian gland carcinoma of the eyelid,[13] vulvar extramammary Paget's disease,[38] and penile erythroplasia of Queyrat.[32] Other indications for Mohs' surgery include certain cases of gangrene, warts, and ulcers.[13,28]

Mohs was the first to apply these techniques to noncutaneous neoplasms of the head and neck when he treated parotid tumors using the fixed-tissue technique.[28] Since then, these techniques have been used to treat squamous cell carcinomas of the floor of the mouth, the tongue, palate, tonsillar pillars, and the paranasal sinuses.[13,39] Conventional surgical treatment of these tumors is often debilitating, with loss of the mandible, tongue, or orbital structures. An interdisciplinary approach combining conventional surgical management of regional metastases with total microscopically controlled excision of the primary tumor is gaining acceptance.[2,17,40] This application of Mohs' micrographic surgery has resulted in preserving the mandible, tongue, and orbits of patients who would have lost these structures if approached by conventional methods.[13]

*References 10, 16, 19, 21, 28, 30, 33, 35, 36.

Report of a Case

The patient, a 62-year-old man, presented to his referring dermatologist with a slowly growing, painless, 0.6-cm pearl-colored papule of the left medial canthus; a similar lesion was also noted on the left cheek. The left cheek lesion, a basal cell carcinoma, was excised primarily with clear margins. The location of the medial canthal lesion, also a basal cell carcinoma, prompted referral for Mohs' surgery.

A presurgical examination showed a 0.6-cm by 0.8-cm healing scar of the left medial canthus (Figure 2). After the lesion was outlined, the skin was infiltrated with a local anesthetic (1.5 ml of a solution of 1% lidocaine hydrochloride with epinephrine at a dilution of 1:100,000), cleansed, and draped. A first layer of tissue was excised with a 2.5-mm margin. Before the specimen was completely excised, superficial reference nicks were made into both the specimen and adjacent skin. The location, size, and shape of the excised

Figure 2.—A biopsy was taken of a basal cell carcinoma just medial and slightly superior to the left medial canthus.

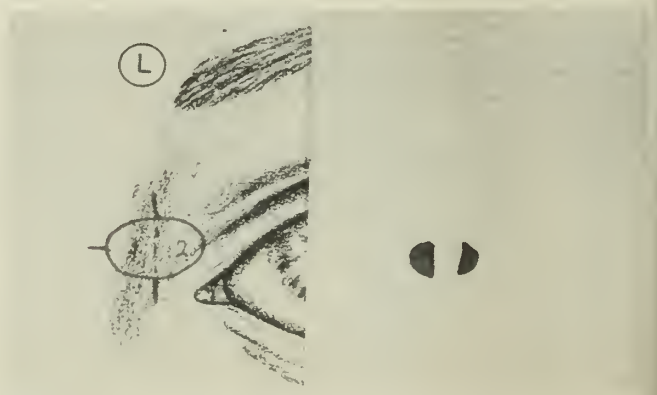

Figure 3.—A schematic map shows the anatomic location, size, and shape of the specimen; the position of the reference nicks; and the size, shape, and color coding of the edges of the cut sections of the specimen.

tissue and the position of the reference nicks were carefully diagrammed on an anatomic map. The surgical specimen was bisected, the cut edges were stained with dyes, and the size and shape of the cut sections and the color code for the marked edges were noted on the map (Figure 3). Horizontally oriented frozen sections were then taken along the entire flattened undersurface, ensuring that all surgical margins, including the epidermal edge, were visible for histologic review. The sections were stained with hematoxylin and eosin and reviewed by the surgeon.

Two foci of residual tumor were noted, and their positions within the tissue were carefully indicated on the map (Figure 4). The reference nicks in the patient's skin were used to relate the location of residual tumor on the map with the anatomic location in the surgical field. An additional layer was taken only around the residual tumor, and a second map was made of this excised specimen. The tissue was processed as before, and microscopic review revealed no residual tumor (Figure 5). The final tumor-free surgical defect measured 1.8 by 1.6 cm (Figure 6) and was allowed to heal by second intention.

Conclusions

Mohs' micrographic surgery offers meticulous marginal control for the treatment of a subgroup of basal cell and squamous cell carcinomas and may also be applicable for various other cutaneous and paracutaneous neoplasms. Its primary advantages are the conservation of normal surrounding tissues and structures, an extremely high cure rate, its use as an outpatient procedure, and a low operative risk. In most instances, a tumor-free defect can be reconstructed immediately. With better understanding of the Mohs technique and the indications for its use, an interdisciplinary team approach to selected cutaneous and paracutaneous tumors combining the surgeon doing the micrographic procedure and the head and neck surgeon, plastic surgeon, or ophthalmologist may become more commonplace.

Figure 4.—The location of residual tumor is indicated on the map. The histologic slides, corresponding in size and shape to the sections on the map, are also shown.

Figure 5.—The map of the second layer of the Mohs micrographic surgery and the corresponding histologic slide show clear margins. Note that only tissue around the residual tumor shown in Figure 4 was removed.

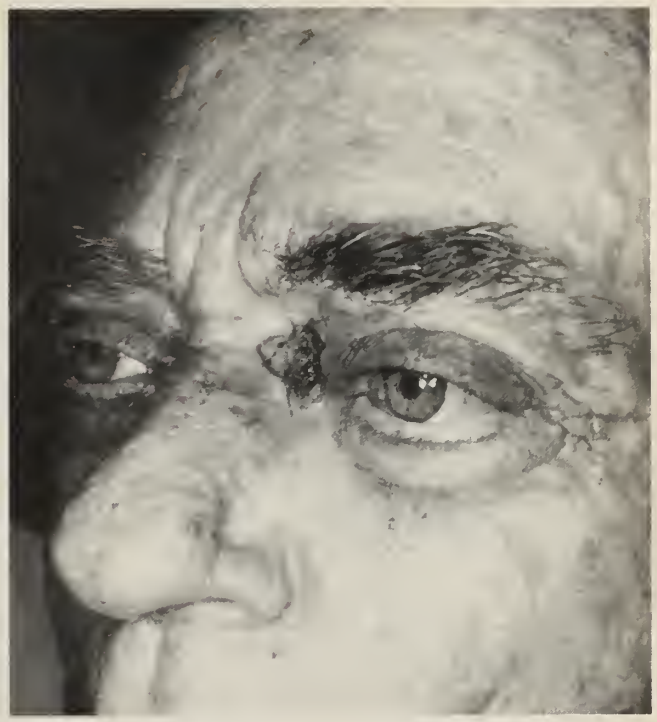

Figure 6.—The final defect is shown following two stages of Mohs' microscopically controlled surgery.

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Medical Progress

Amnestic Disorders

Pathophysiology and Patterns of Memory Dysfunction

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A wide variety of conditions seen in medical practice can produce memory impairment (amnesia). Normal aging, depression, and anxiety are commonly associated with memory difficulties, as are many neurologic conditions. Systemic illnesses can impair memory by injuring vulnerable limbic regions sensitive to hypoxia or hypoglycemia. Commonly used over-the-counter and prescription medications can likewise cause amnesia.

These conditions disrupt memory in characteristic ways. Recent studies suggest that immediate, recent, and remote memory functions have different neuroanatomic substrates, as do the processes of registration, retention, and retrieval. New classifications have emerged to explain the evidence for multiple memory subsystems. The neuropharmacology of memory now includes several peptides in addition to cholinergic and noradrenergic pathways. Critical limbic regions have been discovered that mediate memory consolidation, and neuronal mechanisms such as long-term potentiation are being implicated in the unique capacity of these areas to permit new learning to take place.

(Erickson KR: Amnestic disorders—Pathophysiology and patterns of memory dysfunction. West J Med 1990 Feb; 152:159-166)

Research into human and animal memory has expanded at an enormous rate in recent decades, spanning fields from epidemiology and psychology to single-cell neurophysiology and molecular biology. Once considered a unitary phenomenon, human memory is now thought to involve a number of distinct and interrelated processes. These differ as to their role in information storage and retrieval, neuroanatomic and neurochemical substrates, and vulnerability to various pathologic conditions.

Amnesia refers to a specific deficit in new learning and memory. Retrograde amnesia indicates a loss of memory for events before the onset of the lesion or condition, whereas anterograde amnesia refers to an inability to acquire new information or experiences occurring during the period of the impairment.[1] Amnestic disorders can occur in isolation, but in practice they are most commonly seen within the more global syndromes of delirium or dementia.[2] The cardinal features of delirium include a fluctuating level of consciousness, impaired attention and concentration, disorientation, and frequently hallucinations and delusions. Delirium may develop acutely or subacutely and is a medical emergency, often precipitated by potentially life-threatening conditions. Dementia refers to a chronic—static or progressive—impairment in intellect with a clear sensorium. In addition to memory impairment, the dementia syndrome includes at least one additional area of cognitive dysfunction, such as agnosias, dyspraxia, dysgraphia, dyscalculia, impaired abstraction, impaired judgment, expressive or receptive language deficits, or visuospatial perceptual difficulties.[3] In this review I focus primarily on "pure" amnestic disorders occurring in isolation but will also discuss memory loss associated with dementia.

Terms and Definitions

The classification of memory into its component processes continues to evolve, and the concepts outlined here include only those having a broad consensus in the current literature (Table 1). Information can be viewed as passing through several storage "buffers" of differing capacity and duration.[4,5] Sensory memory persists for around 250 milliseconds in the visual mode (iconic memory) and 1 to 2 seconds in the auditory mode (echoic memory). For example, the visual icon is responsible for the afterimage one sees after shifting gaze from a picture or item to a blank background. Immediate (short-term, primary) memory has a duration of around half a minute, and extensive studies indicate a limited capacity of seven (plus or minus two) items for this buffer, whether the items be numbers, names, visually presented items, or other "units" of information. This buffer is commonly tested by the digit span (or Corsi blocks for nonverbal span). It is highly vulnerable to distraction, requiring attention and vigilance to maintain the content. As an example, if a person's attention is distracted while holding a telephone number in immediate memory, the number is usually lost.[4]

Recent (secondary) memory is called "short term" in many clinical studies and "long term" in most studies by cognitive psychologists. This has a duration of minutes to weeks or months and exhibits a much larger storage capacity than immediate memory. Generally, information must have been consciously attended to before it can enter recent

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ABBREVIATIONS USED IN TEXT

ACTH = adrenocorticotropic hormone
CNS = central nervous system

memory. On entering this buffer, information undergoes a process of consolidation of variable duration. Recent memory is commonly tested by presenting a person with three unrelated words or objects and testing his or her recall for these items after a 2- to 5-minute distraction period. Deficits in the consolidation process that lead to an impairment of recent memory are the cardinal feature of amnestic disorders and occur in a wide range of conditions, which will be discussed further.

The remote (long-term) memory buffer stores information lasting from months to a lifetime and contains a vast array of personal experiences and knowledge about the world. Information passes into this buffer after it has been sufficiently consolidated. Controversy exists as to whether information in remote memory is stored indefinitely or eventually fades or becomes distorted.

Three elementary operations govern memory function: registration, storage, and retrieval. Registration refers to the "encoding" or acquisition of information and generally requires intact attentional resources and conscious effort. Retention (storage or consolidation) refers to the ability to store information over time in an intact form. Retrieval (decoding, recall) processes involve the ability to retrieve stored information. As with registration, retrieval generally requires conscious (volitional) processes.[6-8]

Registration is tested by having the subject repeat or respond to information immediately on its presentation. After a distraction task, the retrieval process is measured by having the subject recall this information. In free recall—the most accurate assessment of the basic retrieval ability—the subject receives no hints or assistance. In cued recall, various types of cues and hints are provided, such as the item's category, function, physical attributes, or other clues. The subject's ability to benefit from such cues partially depends on whether similar cues were identified during the registration of the information. To measure information retention (storage), it is necessary to bypass the retrieval process by the use of recognition tasks, in which the original information is presented along with several other items (multiple choice), one other item (forced choice), or alone (yes or no). In normal and amnestic subjects, recognition tasks typically yield higher scores than free or cued recall, indicating that much information is retained that cannot be readily retrieved. These processes have been extensively studied in the amnestic disorders and will be frequently referred to below. Free recall, cued recall, and recognition all are examples of explicit memory tasks—that is, they require conscious, volitional processes. Storage can also be assessed by implicit memory tasks, in which more automatic processes are involved. These tasks include priming, in which the speed, accuracy, or type of response to a word is affected by a word presented immediately before it; word-stem completion, in which the first letter or syllable of a word is presented and the subject asked to complete it; or word-fragment completion, in which parts of a word are presented and the subject asked to complete it. Implicit memory processes are an even more robust measure of storage, and amnestic patients often display intact implicit memory in the face of disrupted explicit memory.[6,7]

TABLE 1.—*Memory Processes: Classification and Neuroanatomy*

Type	*Neuroanatomic Substrate*
Sensory	
Iconic (visual)	Visual (occipital) cortex
Echoic (auditory)	Auditory (temporal) cortex
Immediate (primary)	Perisylvian cortex, frontal lobe
Recent (secondary)	
Declarative (explicit)	Retention: medial temporal lobe
Episodic (events) Semantic (facts)	Registration and retrieval: mamillothalamic tract and dorsomedial thalamic nucleus
Procedural (implicit)	
Motor skills	Cerebellum
Perceptual skills	Sensory association cortex
Cognitive skills	Unknown
Priming	Unknown
Remote	Appropriate association cortex

Several broad memory classifications have emerged that deserve mention, as they are frequently used in the literature: "working" versus "reference" memory,[9] "episodic" versus "semantic" memory,[10] and "declarative" versus "procedural" memory.[11-14] Reference memory can be likened to a filing cabinet containing recent and remote information gained from previous experience. Working memory refers to that which is being actively updated by the current experiment or experience (similar to primary memory). This can be likened to a mental desktop. Episodic memory contains information about events occurring in a specific place and time, such as what happened last Christmas, whereas semantic memory houses "eternal" facts, principles, associations, and rules about the world (such as what the meaning of Christmas is, the capital of Russia, the number of hours in a day, and so forth).[10] Investigators studying human amnesia argue that little support exists for the above distinctions on physiologic grounds and that a more anatomically robust distinction is that of declarative versus procedural memory systems.[11,14] Declarative memory pertains to facts about the world and past personal events that must be consciously retrieved to be remembered. Procedural memory, in contrast, is involved in learning and retaining a skill or procedure, such as how to ride a bicycle, follow the basic rules of a board game like chess, or get dressed. Such abilities become "automatic" and do not require conscious direction. Amnestic patients show an intact ability to acquire new skills at almost normal rates (procedural) but are unable to recall having engaged in the task before (declarative).

A final distinction that should be described is that popularized by Squire, between diencephalic and medial temporal amnesia.[14] Diencephalic amnesia occurs in alcoholic patients with Korsakoff's syndrome, who suffer from damage to the mamillary bodies and dorsomedial nucleus of the thalamus (mamillothalamic tract). It is characterized by impaired registration (encoding) and retrieval (decoding), but consolidation or retention is grossly intact. Thus, if given registration or retrieval aids such as the use of an associated word or an item's category, these patients can perform almost as well as normal subjects after hours to weeks. Frontal lobe damage may be present in most of these patients.[12] In medial temporal lobe amnesia, registration and retrieval are intact, but

there is a marked deficit in consolidation resulting in an abnormally rapid forgetting rate.[1,2,15]

Specific Amnestic Disorders

A wide range of psychiatric, neurologic, and systemic conditions can produce amnestic disorders, isolated or in combination with the dementia syndrome.[1-3,8,15,16]

Age-Related Memory Changes

By the year 2030, the proportion of our population older than 65 years will have increased from its present 11% to 20%. As many as two thirds of older persons experience mild difficulties in recalling names, numbers, and other facts, termed "benign senescent forgetfulness."[17] In fact, a syndrome of age-associated memory impairment has recently been proposed with the following diagnostic criteria: age 50 years or older, memory scores on tests of secondary (recent) memory of at least 1 standard deviation below the mean compared with young adults, an absence of other areas of cognitive decline or of fluctuating levels of consciousness, and the exclusion of causative physical factors.[16,18] Most of these cases do not have dementia on five-year follow-up.[18]

Psychiatric Conditions

Severe anxiety disorders, bipolar manic and depressive episodes, unipolar depression, and schizophrenia can impair memory by causing distractibility, impaired attention and concentration, and inadequate processing of new information.[19] The pseudodementia of depression can be difficult to distinguish from organic dementias, as prominent features include variable forgetfulness, a slowing of mentation, deficits in attention and concentration, and concrete thinking with impaired problem-solving ability.[19,20] As these factors clearly affect effortful cognitive processes, it is not surprising that recognition memory, which reflects retention, is less impaired in depression than is free recall, an effortful retrieval process.[21,22] Psychogenic amnesia, fugue, and multiple personality disorder are dissociative anxiety states in which a person forgets important personal information (psychogenic amnesia) or adopts an entirely new identity for a period of time (fugue and multiple personality).[23] A key feature helping to distinguish these patients from those with organic amnestic disorders is that they are able to learn and acquire new information at a normal rate during an episode—that is, there is no anterograde memory loss.

Neurologic Disorders

Alzheimer's disease. This disorder affects 4% of persons older than 65 and reaches a 20% prevalence by age 80.[24] The most frequent initial complaint is of impaired memory for recent information and events.[25,26] The memory disorder of Alzheimer's disease is complex and varies with the stage of the disease.[6,24-31] In the early stages, it can be difficult to distinguish from age-associated memory impairment, and recognition scores may be considerably stronger than free recall scores—indicating retrieval deficits in the face of relatively intact retention of information. Immediate (primary) memory is often normal in the early stages. As the dementia progresses, a more profound amnestic disorder sets in that is unaided by retrieval cues and includes deficits in immediate and remote memory in addition to the severe recent memory impairment. Researchers disagree on the relative contributions of registration, retention, and retrieval deficits to the memory loss seen in these later stages.[6,27] There is a growing consensus, however, that a deficit in semantic memory processes (defined earlier) appears early, progresses, and underlies much of the episodic memory failure in patients with Alzheimer's disease.[6,27] Patients show deficits in forming associations to new information (such as providing synonyms, item category, or item function) and show little to no benefit from semantically structured presentation of information (such as listing words by their category groups).

Pick's disease. In Pick's disease, which has a prevalence of approximately 2% of cases of Alzheimer's disease, the frontal and temporal lobes are predominantly affected. In the early stages, memory loss is not as pronounced as in Alzheimer's disease, whereas personality alterations—due to involvement of the frontal lobes—are more striking.[15] As the disease progresses, however, and as medial temporal lobe involvement increases, memory deficits become prominent as well.[1]

Parkinson's disease. Several extrapyramidal disorders are associated with memory impairment. Three of these—Parkinson's disease, Huntington's disease, and Wilson's disease—will be discussed. The estimated prevalence of dementia in Parkinson's disease ranges from 10% to 40%, depending on study design and selection methods.[32] The deficits chiefly comprise a slowing of mentation and difficulty initiating or maintaining effortful processes including memory registration and retrieval.[29,33,34] In contrast, retention-consolidation processes may be intact or only mildly impaired, as reflected in superior recognition scores relative to recall scores.[29] The degree of cognitive impairment correlates strongly with the extent of motor involvement,[33] and in lateralized parkinsonism the neuropsychological deficits—including memory dysfunction—reflect the side of greatest motoric compromise.[34] Older patients have a higher prevalence of dementia.[32,33] The relative contributions of the dopaminergic nigrostriatal deficits and of Alzheimer-like lesions often found in the brains of demented patients with Parkinson's disease is currently undergoing debate.[32-34]

Huntington's disease. Patients with Huntington's disease may exhibit clear neuropsychological impairment several years before overt motor manifestations develop,[35] and several well-controlled studies indicate that memory is the first area to be affected.[36] Here, as in Parkinson's disease, the greatest deficits occur in the registration and retrieval processes, while milder compromises are seen in consolidation. In contrast with those with Parkinson's disease, however, patients with Huntington's disease appear much less able to benefit from memory cues, apparently because of profound deficits in registration (acquisition, or encoding).[36] Also, a large study of immediate memory using verbal (digit span) and nonverbal (Corsi block) measures showed that patients with Huntington's chorea scored considerably lower than patients with either Parkinson's disease or progressive supranuclear palsy.[37]

Other extrapyramidal disorders. Mild to moderate memory deficits with little to no associated cognitive impairment have been recently described in two other disorders that can present with extrapyramidal features: Wilson's disease (hepatolenticular degeneration)[38] and olivopontocerebellar atrophy.[39] Medalia and co-workers and Kish and associates did not attempt to distinguish the roles played by registration, consolidation, or retrieval processes, however.[38,39]

Cerebrovascular disease. This disorder can produce a

variety of amnestic syndromes, depending on which central nervous system structures are affected. The posterior cerebral artery supplies the occipital lobe and medial temporal lobe, and infarctions in this distribution produce homonymous hemianopsia along with an anterograde and retrograde amnesia, impairing memory consolidation processes. The amnesia is particularly severe when bilateral infarctions occur.[1] The confusional state resulting is largely based on the anterograde memory loss, but deficits in focal attention and loss of linguistically organized memory (when the dominant lobe is affected) have also been reported.[40] In the thalamus, infarctions in two locations can lead to anterograde amnesia, which is frequently coupled with confusion and confabulation, particularly when the infarcts are bilateral. The first involves the paramedian area, including the dorsomedial thalamic nucleus and internal medullary lamina.[41-43] The second affects the anterior thalamic nucleus and the mamillothalamic tract that reciprocally connects it with the mamillary bodies.[42] This latter area is precisely where the lesions of Korsakoff's syndrome occur, and it is significant that confabulation is also prominent in patients with this condition (to be discussed further).

Infarctions in the subthalamic and mesencephalic regions frequently induce impaired attention and mental control, with slowing of verbal and motor responsiveness. These deficits are probably due to a complex mixture of damage to fibers of the ascending reticular activating system traveling through the medial thalamus and of damage to specific ascending monoaminergic pathways arising in the medial brain-stem tegmentum.[43] The result is prominent deficits in concentration, registration, and retrieval. One noteworthy case of combined anterograde and retrograde amnesia was recently reported in a 39-year-old man following hemorrhage from an arteriovenous malformation into the splenium of the corpus callosum.[44] Although this lesion spared important memory structures (hippocampus, thalamus, basal forebrain, and fornix), it effectively dislocated the anterior thalamus from the hippocampus by involving interconnecting projection fibers between these two key limbic structures.

Transient global amnesia, while not associated with an increased risk of infarctions, may be due to transient ischemia in the posterior cerebral artery distribution. The condition occurs in middle-aged or older patients of both sexes and is characterized by a suddenly impaired memory without associated neurologic findings. Recovery is complete within 24 hours, but during the episode the patient displays a profound anterograde and retrograde amnesia in a clear sensorium. Immediate memory is normal (repetition of verbal and nonverbal material is intact), but the patient may appear confused owing to the loss of secondary (recent) memory function, as recall for material after a several-minute delay is absent. The retrograde amnesia extends to events and memories anywhere from hours to years before the episode. After the episode resolves, permanent amnesia for the episode itself remains.[45-47]

Epilepsy. Studies of patients with intractable epilepsy show that those with complex partial seizures (also called "temporal lobe" or "psychomotor" seizures) have deficits in memory, learning, and attention.[48] Material-specific memory deficits have been described—that is, verbal memory is particularly impaired when the dominant medial temporal lobe is involved, and nonverbal memory when the nondominant side contains the primary seizure activity.[49] Registration processes appear intact, as does immediate memory. The primary deficit appears to occur in the retention or consolidation phase of memory, as shown by impaired performance on recognition as well as recall tasks and by rapid rates of forgetting.[48]

Patients with Korsakoff's syndrome from alcohol-associated thiamine deficiency experience anterograde and retrograde amnesia. The critical underlying lesion appears to be damage to the mamillothalamic tract and dorsomedial thalamic nucleus. The retrograde amnesia extends backward 3 to 20 years before the amnesia began.[15] The condition is distinct from alcoholic dementia in which deficits in attention, word-list generation, abstraction, and constructions accompany the memory impairment.[15] In patients with Korsakoff's syndrome, the anterograde amnesia results primarily from an acquisition (registration) disorder, rather than a failure of retention.[14,31] Of interest, these patients frequently exhibit confabulation (memory falsifications) thought to be associated with injury to the medial frontal lobes and mamillothalamic tract.[50]

Multiple sclerosis. Memory is one of the most consistently impaired cognitive functions in patients with multiple sclerosis. Immediate (short-term) memory capacity as measured by digit span appears grossly intact, but retrieval of verbal information from secondary (long-term) memory is impaired, as measured on tests such as paired-associate word recall and logical memory for paragraphs.[51] This may be due to impaired working memory—specifically, to a defect in what Baddeley calls the "articulatory loop," the speech-based temporary store that allows short-term retention through subvocal rehearsal.[5] In addition, patients exhibit slowed information processing on tests that require encoding of complex information under speeded conditions.[52] These observations, coupled with normal forgetting rates, suggest that the predominant memory function affected is that of acquisition (registration). Patients with the chronic progressive form of multiple sclerosis may have relatively greater deficits in recognition tasks than other patients with multiple sclerosis, but even here the evidence points largely to an impairment of acquisition (registration) processes rather than to retention (consolidation) dysfunction.[53]

Head injury. The most frequently reported cognitive complaint following head injury is memory impairment. At one-year follow-up of 102 patients with head injury in a large longitudinal study,[54] the measures least affected were those assessing concentration (mental control), orientation, and immediate memory (digit span forward). Most affected were tasks requiring recent memory (logical memory for paragraphs, delayed recall, and difficult pairs of word associates). Indices of recognition were the most robust, and retrieval was the most vulnerable.

According to a survey study of 1,088 male college students,[55] the extent to which retrograde amnesia persists following head injury appears related to the duration of the posttraumatic period of anterograde amnesia. In cases where the posttraumatic amnesia lasts over an hour, more than 50% of subjects exhibit long-lasting retrograde amnesia. During the period of posttraumatic amnesia, subjects matched to controls on the acquisition of information (by providing them with longer stimulus exposure times) showed accelerated rates of forgetting over 32 hours.[56] This impairment in memory consolidation is not surprising, as the brain regions most susceptible to contusion are the temporal poles and the

orbitofrontal surface, as well as long fiber bundles such as the fornix. Therefore, limbic and paralimbic areas are especially vulnerable to head trauma.[1]

Other conditions. Herpes simplex encephalitis often damages limbic structures to the exclusion of other areas of the central nervous system (CNS). With its predilection for the medial temporal lobe (amygdala, hippocampus, and parahippocampal gyrus) and orbitofrontal structures, the virus causes an anterograde amnesia characterized by intact immediate memory and registration processes but impaired recent memory or consolidation function.[1,15] Compared to patients with Korsakoff's psychosis, patients with herpes simplex encephalitis have less confabulation, more awareness of their deficits, and less improvement with memory cues.[57]

Space-occupying CNS lesions such as tumors and abscesses can produce amnesia in a variety of ways. They act both through their local effects on various parts of the limbic system—basal forebrain, mamillothalamic tract, and medial temporal lobe—and by exerting pressure on distant structures through increased intracranial pressure and edema. Tumors in the walls and floors of the third ventricle are most likely to cause an amnestic syndrome, being immediately adjacent to the thalamus.[1,15]

Obstructive hydrocephalus can either be noncommunicating—owing to blocked flow from the ventricular system into the subarachnoid space—or communicating—from impaired absorption of cerebrospinal fluid by the pacchionian villi of the subarachnoid space. In either case, clinical characteristics include dementia, gait disturbance, and incontinence. The dementia features include slowed mentation and a decreased capacity for effortful memory functions such as registration and retrieval.[15] Table 2 provides a summary of some of the disorders just described and their known pathophysiology.

Systemic Conditions

Memory impairment is seen in association with a host of systemic diseases. Most often, it is accompanied by the broader syndromes of delirium or dementia. Relatively isolated memory loss, however, can occur from medical disease through one of two mechanisms: impaired memory consolidation from medial temporal lobe dysfunction, or in deficits in registration and retrieval processes through effects on the thalamus or frontal lobes.

Hypoxia can cause either type of deficit. When it is severe and short-lived, only those areas of the brain most vulnerable to an acute lack of oxygen are permanently affected. Thus, damage is often greatest to the hippocampus, and a permanent defect in new learning and memory consolidation (anterograde amnesia) results.[58] Cardiopulmonary arrest, acute respiratory failure, anesthetic accidents, carbon monoxide poisoning, drowning, strangulation, and other conditions that induce acute hypoxemia can produce this type of memory loss.[1,15] If the hypoxia is severe or prolonged, more widespread neuropsychological deficits occur, including apathy, attentional difficulties, and a dementia syndrome.[1,15] Chronic or recurrent hypoxia of moderate severity resulting in this more widespread impairment is seen in many patients with chronic obstructive pulmonary disease.[59] Acute hypoglycemia also has its greatest impact on hippocampal function, and subacute or recurrent episodes of acute hypoglycemia—such as may occur in poorly controlled insulin-dependent diabetes mellitus—can produce a relatively "pure" amnestic syndrome.[60]

TABLE 2.—*Selected Amnestic Disorders and Their Pathophysiology*

Disorder	*Physiologic Substrate for Amnesia*
Alzheimer's disease	Neuronal loss in nucleus basalis of Meynert
	Loss of acetylcholine and choline acetyltransferase activity in septohippocampal pathway
	Neurofibrillary tangles in CA1 and CA3 pyramidal cell regions of hippocampus
	Neuritic plaques in dentate gyrus
	Neuronal loss in entorhinal cortex, layers II and IV
Korsakoff's syndrome	Thiamine deficiency-induced lesions in dorsomedial nucleus of the thalamus, mamillary bodies, mamillothalamic tract
Transient global amnesia	Transient ischemia to hippocampus and other medial temporal lobe regions
Head trauma	Injury to hippocampus and other medial temporal lobe regions
Herpes simplex encephalitis	Viral attack on limbic regions including medial temporal lobe and cingulate gyrus
Partial complex epilepsy	Possible damage to CA3 region
Infarction, anoxia	Damage to medial temporal lobes or thalamus

Neurochemistry and Neuropharmacology of Memory

In normal subjects, anticholinergic agents—particularly muscarinic blockers such as scopolamine—appear to mimic the type of learning and memory deficits seen in Alzheimer's disease.[61,62] The majority of cholinergic fibers supplying the cortex and hippocampus emanate from cells in the nucleus basalis of Meynert. Cell loss in this region and profound reductions in choline acetyltransferase activity in the septohippocampal pathway have been found in brains from patients with Alzheimer's disease.[63,64] The aspects of learning and memory affected by cholinergic pathways appear to be somewhat controversial. They include memory consolidation,[61,63,65,66] registration, and retrieval processes[67] as well as attentional processes.[68] Atropine, scopolamine, belladonna, and the antihistamines are active ingredients in many over-the-counter and prescription sleeping agents, antiparkinsonian medications, and a number of antidepressant and antipsychotic medications.[69] Thus it is not surprising that such agents are often noted to impair memory and concentration, particularly in the elderly or demented.

Numerous studies of animals have implicated catecholaminergic systems in learning and memory processes.[63,70] Drugs disrupting these systems disrupt memory storage, whereas agonists produce dose-dependent facilitation at a restricted range (window) of dosages.[71-73] Although numerous changes in catecholamine systems occur in humans with age, their relationship to age-associated memory impairments has not been established. In particular, the use of adrenergic stimulants such as methylphenidate hydrochloride (Ritalin) has not been shown to improve memory performance in the aged.[63]

Benzodiazepines can exert a direct amnestic effect in an otherwise clear sensorium.[63] Lorazepam is particularly implicated in this regard.[74] A study of diazepam use found that the major memory subsystem impaired by benzodiazepines

is the declarative memory system and that the procedural memory system is spared.[75] The neuroanatomic sites of action of the benzodiazepines are heterogeneous, and binding sites have been shown to exist in several limbic regions.[76]

In recent years, neuropeptides of hypothalamic and pituitary origin have been increasingly implicated in learning and memory processes.[63] Adrenocorticotropic hormone (ACTH) and vasopressin analogues improve memory and learning performance in animals and humans. It has been suggested that ACTH affects motivation and attention and that vasopressin is more directly related to memory processes.[63] Elderly patients given lysine vasopressin in nasal spray form did better than those given placebo on tests of attention, concentration, and memory.[77,78] Mildly demented aged subjects likewise seem to show benefit from the use of desmopressin acetate (1-deamino-8-D-arginine vasopressin; DDAVP),[79] whereas more severely demented patients show no benefit.[80] The administration of ACTH does not reduce the memory impairment seen in aged subjects; it may instead exert its effects on mood and attentional processes.[63] Neuropeptide Y, a 36-amino-acid peptide occurring in highest concentrations in the hippocampus and amygdala, has recently been reported to alleviate amnesia induced by scopolamine and by protein-synthesis inhibitors in mice.[81]

Neuroanatomy and Neurophysiology of Memory

The role of the hippocampus, thalamic nuclei, and mamillary bodies in providing the neural substrate necessary for acquiring and retaining new information has been alluded to (Figure 1). It is unlikely that these structures in themselves contain specific memories, but in some way they provide a means to store and to retrieve memories, particularly those that are undergoing consolidation. The most extensively studied of these limbic regions is the hippocampus. Since the famous case of H.M., a patient who showed severe anterograde amnesia following bilateral amygdalohippocampectomies for seizure control in 1956,[82] a huge volume of research in humans and animals has sought to define the hippocampal role in memory.

A critical pathway by which information from the cortical association areas reaches the hippocampus is through the entorhinal cortex located at the anterior pole of the parahippocampal gyrus. Moreover, the amygdala, which receives impulses from large cortical, hypothalamic, and basal forebrain areas, has extensive projections to the entorhinal cortex.[83,84] Cell bodies in layers II and III of the entorhinal cortex receive the majority of these projections and send fibers through the perforant pathway to the dentate gyrus of the hippocampus. The dentate granule cells, in turn, send mossy fibers that synapse on apical dendrites of the CA3 cells of the hippocampus. Cells of the dentate gyrus appear capable of integrating recently acquired information.[85] Interestingly, in patients with Alzheimer's disease, neurofibrillary tangles develop in the cells of origin of the perforant pathway (layers II and III of entorhinal cortex), and neuritic plaques develop in the outer layer of the dentate gyrus, effectively disconnecting the hippocampus from the association and limbic cortices.[83] Further, CA1 pyramidal cells, which receive fibers from the CA3 cells and serve as the major output from the hippocampus, are themselves extensively affected by neurofibrillary tangles. Layer IV of the entorhinal cortex, which receives a strong projection from the hippocampus and projects to widespread cortical regions, is also damaged.[83] The hippocampus is thus effectively disconnected from its major incoming and outgoing pathways in Alzheimer's disease (Figure 2). These observations, coupled with the profound reductions in choline acetyltransferase activity in the septohippocampal pathway[64] and the extensive loss of cholinergic neurons in the nucleus basalis of Meynert,[86] may serve to explain why the most common and predominant complaint in patients with Alzheimer's disease is of an anterograde amnesia for new information and recent events.

A candidate physiologic mechanism for the consolidation of new memories within the hippocampus is that of long-term potentiation.[87] This refers to a stable, relatively long-lasting increase in the magnitude of a postsynaptic response to a constant afferent volley, following brief tetanic (high-frequency) stimulation of those afferents.[88] While long-term potentiation has only been elicited by electrical stimulation and not by natural phenomena, several features suggest that it may represent a model for, or use the same underlying neuronal apparatus as, learning and memory.[89] Parallels between learning-induced increases in hippocampal neuronal

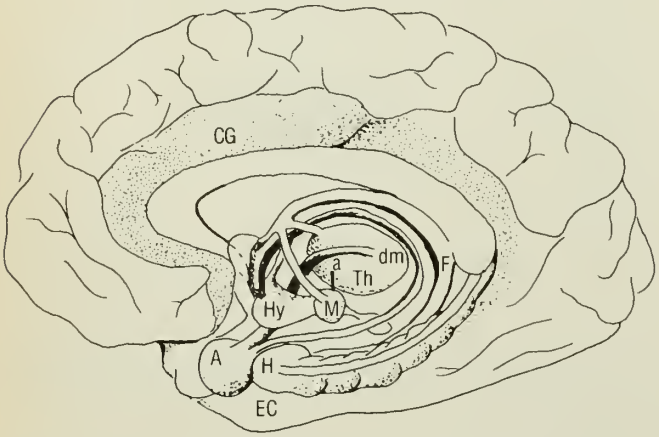

Figure 1.—The drawing shows the limbic areas involved in memory: **A**, amygdala; **a**, anterior thalamic nucleus; **CG**, cingulate gyrus; **dm**, dorsomedial thalamic nucleus; **EC**, entorhinal cortex; **F**, fornix; **H**, hippocampus; **Hy**, hypothalamus; **M**, mamillary body; **Th**, thalamus.

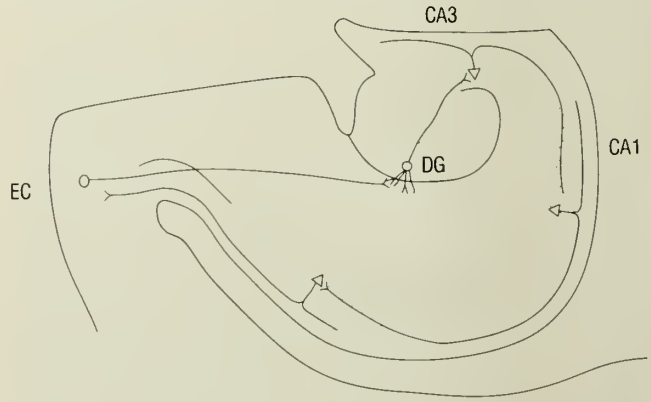

Figure 2.—The critical hippocampal memory pathways are shown: (1) The cell body in layer II of the entorhinal cortex **(EC)** projects through the perforant pathway to the outer layer of the dentate gyrus **(DG)**; (2) a dentate granule cell sends mossy fibers to synapse on a CA3 pyramidal cell; (3) the CA3 cell sends an axon to synapse with a CA1 pyramidal cell; (4) the CA1 pyramidal cell sends an axon to synapse on a cell in the subiculum; and (5) the subiculum cell sends a projection to layer IV of the entorhinal cortex. The dots (stippled area) indicate regions of cell bodies.

activity and long-term potentiation include the observations that both

- Are exhibited by pyramidal neurons in the hippocampus;
- Require only a small number of stimuli (electrical pulses or stimulus presentations) for induction;
- Develop over a similar time course (hours to days);
- Exhibit a similar magnitude of increase over baseline;
- Depend on a specific range of stimulus frequencies; and
- Persist for long periods of time.

The induction of long-term potentiation requires nearly simultaneous activation of the presynaptic membrane and postsynaptic depolarization (Figure 3). This coincident activity results in an influx of calcium ions into the postsynaptic dendritic spine. This influx is mediated by voltage-dependent *N*-methyl-D-aspartate receptors, which at the resting membrane potential are blocked by magnesium.[88,90] Sufficient depolarization of the membrane—which is provided by the combined presynaptic activation and postsynaptic depolarization from earlier tetanic stimulation—removes this voltage-dependent block.[90] The necessity for near-simultaneous activation of presynaptic and postsynaptic elements accounts for the associative (learning) nature of long-term potentiation.

Declarative and procedural memory are two broad subdivisions of recent (secondary) memory processes. Most scientific investigation has been directed at the limbic structures necessary for declarative memory. Their integrity is best measured by using explicit memory tasks. Recent studies, however, have begun to focus on the neural substrates for procedural memory. While this form of memory is complex and likely to involve multiple CNS sites including motor and method-specific sensory cortex, evidence is mounting for a critical role for the cerebellum in helping to mediate many types of procedural (implicit) memory tasks.[91]

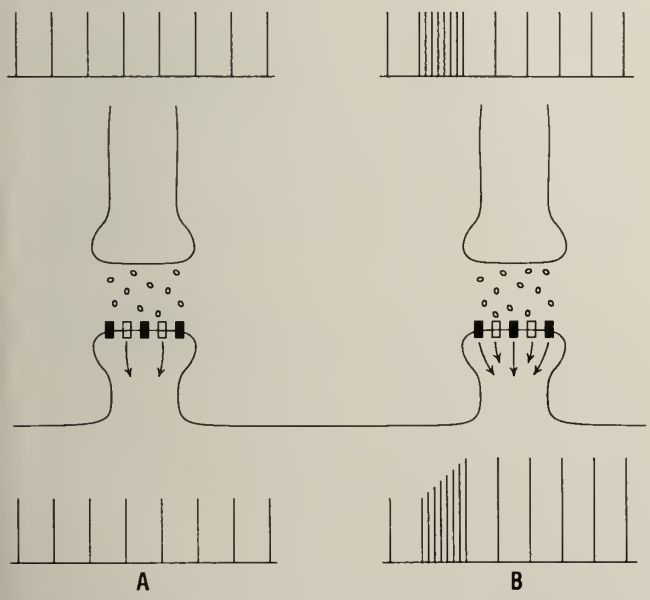

Figure 3.—This diagram of long-term potentiation and *N*-methyl-D-aspartate (NMDA) receptors shows two separate mossy fibers (presynaptic membranes), each synapsing onto a different dendritic spine of a CA3 pyramidal cell: (1) The time record of presynaptic stimulation shows a constant-amplitude pulse of invariate frequency in **A**, contrasted with a brief period of rapid tetanic stimulation in **B**; (2) the constant, low-frequency stimulation in **A** opens non-NMDA receptors through the binding of transmitter **(clear rectangles)**, allowing a small, transient depolarization. In **B**, the tetanic (high-frequency) stimulation permits summation of each new depolarizing event with the previous one. This greater degree of depolarization removes the voltage-dependent blockade of NMDA receptors **(black rectangles)** by magnesium, so that each new incoming pulse triggers calcium influx through NMDA as well as non-NMDA receptors; (3) the postsynaptic potential spike is shown as fixed in amplitude for **A**, but in **B** it increases its amplitude markedly during tetanic stimulation and sustains this increase following resuming the normal stimulus train, presumably due to continued opening of the NMDA receptors.

Immediate (primary) memory has been found to require a region distinctly removed from the limbic structures that mediate recent memory. This is the perisylvian cortex surrounding the sylvian fissure, an area also essential for language (digit) repetition. Evidence seems to indicate that remote memories are stored diffusely in multiple brain sites, possibly including secondary and tertiary association cortex.[8]

Conclusion

The field of memory research has now reached the point at which tasks that index selective memory processes are being combined with sophisticated techniques to elucidate the brain anatomy, chemistry, and physiology that underlie these.[92-97] Clinical studies of memory disorders are likewise making use of more precise conceptualizations of what stage of information acquisition, storage, and retrieval is affected by the disease in question.[98-100] It is hoped these advances will provide a basis for improved treatments of amnestic disorders in the future.

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Medical Staff Conference

Peptic Ulcer—An Infectious Disease?

Discussant
WALTER L. PETERSON, MD

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Homer A. Boushey, MD, Professor of Medicine, and Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD*: *Perhaps my training in infectious disease has biased me, but I think that infectious agents may be important in many diseases in which they were once thought to play no role. One such disease is peptic ulcer. Recent evidence suggests that a bacterium,* Campylobacter pylori, *may be important in upsetting the balance between the acid and pepsin in gastric secretions and the defense of the gastric mucosa. We are fortunate to have at this conference Dr Peterson from Southwestern Medical Center, Dallas, to review this potentially important organism and the evidence that it contributes to gastritis, dyspepsia, and peptic ulcer disease.*

WALTER L. PETERSON, MD†: Acid and pepsin are present in abundance in the normal human stomach and duodenum. The epithelial cells of the stomach and duodenum are protected from the damaging effects of acid and pepsin by a "balancing" mechanism of mucosal resistance. As long as this balance remains in effect, epithelial integrity remains intact.

Gastroduodenal Mucosal Resistance

The most important factor in mucosal defense against the damaging effects of acid and pepsin may be endogenous prostaglandins.[1,2] Early work by Robert and co-workers showed that administering prostaglandin compounds beforehand could prevent the damaging effects on rat gastric mucosa of various noxious agents.[3] While it was initially thought that this protective effect was related to the antisecretory effect of prostaglandins, Robert and associates later showed that the same protection occurred at doses of prostaglandins that did not reduce acid secretion.[4,5] The ability of prostaglandins in such doses to prevent damage to rat mucosa from a variety of strong irritants was called "cytoprotection." Similar protection against strong irritants can be afforded by pretreatment with mild irritants, rather than prostaglandins.[6,7] Termed "adaptive cytoprotection," this phenomenon is now believed to be a prostaglandin-independent phenomenon.[8]

Great interest has developed in the mechanisms by which prostaglandins protect gastroduodenal mucosa. Two important effects of prostaglandins are the stimulation of mucous and bicarbonate secretion.[9] A mucous gel acts as a barrier to the damaging effects of pepsin and to the diffusion of hydrogen ions from the gastric lumen. The hydrogen ions that are able to penetrate the mucous gel are thought to be neutralized by endogenously secreted bicarbonate. Thus, in the normal state, the milieu just above the epithelial cells is at or near neutrality.[10]

These are only the first lines of defense, however, and the presence of mucus and bicarbonate does not protect all cells from the effects of various damaging agents. Rather, it is now believed that prostaglandins act primarily to maintain mucosal blood flow during a period of injury, a function that may preserve cells deep in mucosal crypts.[11] These cells can then migrate upward and reconstitute damaged superficial epithelium.[12] Whatever the mechanisms, it seems likely that endogenous prostaglandins play a major role in protecting gastroduodenal mucosa from deep tissue injury by acid or pepsin or other damaging agents, at least in animals. The extent to which prostaglandins protect human mucosa is less well understood.

Whenever the balance between acid and pepsin and mucosal resistance shifts toward acid and pepsin, a peptic ulcer may develop. Stated simply, this shift may occur because of excess levels of acid and pepsin, reduced mucosal resistance, or both. Traditional teaching has emphasized the importance of acid (and pepsin) as the cause of this imbalance. For example, persons with high levels of acid secretion, such as in the Zollinger-Ellison syndrome, have a high incidence of duodenal ulceration, whereas prophylactic treatment with agents that reduce gastric acid secretion, such as the H_2-receptor antagonists, reduces the incidence of recurrent ulcer. It is clear, however, that acid and pepsin alone are, in most instances, inadequate to produce a peptic ulcer. For example, most persons with duodenal ulcer have normal levels of acid secretion,[13] and prophylactic treatment with agents that do not affect acid secretion (such as sucralfate) also reduces the risk of ulcer recurrence.[14]

In summary, while acid and pepsin must be present for an ulcer to form, and while high levels of acid secretion in-

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crease the risk of an ulcer developing, the basic mechanism of ulcer formation probably involves a disruption of mucosal resistance.

Disruption of Mucosal Resistance

Reduction of Endogenous Prostaglandins

In humans, evidence that a depletion of endogenous prostaglandins is important in disrupting mucosal protection remains inconclusive. There are, however, several lines of evidence that suggest this may be true:

- Patients with duodenal and gastric ulcer have diminished capacity to synthesize prostaglandins in antral mucosa[15,16];
- Patients with duodenal ulcer have been shown by Isenberg and colleagues to secrete less duodenal bicarbonate than do normal controls, either in the basal state or in response to stimulation with hydrochloric acid[17];
- Administering nonsteroidal anti-inflammatory drugs (NSAIDs), which are believed to be "ulcerogenic," results in reduced levels of prostaglandins in both gastric and duodenal mucosa and a decreased secretion of duodenal bicarbonate.[15,18] Interestingly, epidemiologic studies suggest that there is an increased incidence of gastric ulcer, but not duodenal ulcer, in patients who take NSAIDs.[19,20]

Thus, the role of prostaglandin depletion in the pathogenesis of peptic ulcer disease remains unsettled. It seems likely that a reduction of prostaglandins plays some role, especially in the pathogenesis of gastric ulcer. The mechanisms by which prostaglandin depletion leads to gastric ulcer formation remain unknown.

Helicobacter pylori Gastritis

Investigators have for many years sought an infectious cause of common gastritis. Although occasional reports in the past noted the presence of spiral bacteria in gastric biopsy specimens, the concept did not gain widespread recognition until 1983. In that year, Warren and Marshall, two investigators from western Australia, published letters in *The Lancet* describing spiral bacteria in patients with chronic active gastritis.[21] Because the organisms were curved they were called *Campylobacter,* and because they were found only on gastric epithelium they were called *Campylobacter pyloridis,* later changed to *Campylobacter pylori.* These investigators soon were able to culture the organism and to begin to define its characteristics. Since then, an enormous amount of work by investigators throughout the world has provided insight into the organism itself, where it is found, how it might be transmitted, and what it may do.

Campylobacter pylori is a gram-negative, microaerophilic organism that, while possessing many characteristics of *Campylobacter* species, is not a true *Campylobacter.* For example, *C pylori* produces abundant quantities of urease, an enzyme not present with other *Campylobacter* species. In addition, an analysis of the genetic composition of *C pylori* shows it to be unrelated to *Campylobacter* species such as *Campylobacter jejuni.* Thus, its name was recently changed from *C pylori* to *Helicobacter pylori.* The organism has a particular predilection for gastric epithelium. Its spiral nature and corkscrew-like motility permit it to penetrate the mucous gel overlying gastric epithelium and to set up residence adjacent and adherent to gastric epithelium. While it is never found on intestinal epithelium, it is found in gastric epithelium in the stomach, in the duodenum in areas of gastric metaplasia, and in the esophagus in patients with Barrett's esophagus. Once found, and unless specifically eradicated by antimicrobial agents, *H pylori* infection is persistent, probably for life.

It is not known how *H pylori* is transmitted, and the organism has yet to be isolated except from human tissues. Nevertheless, several lines of evidence point to person-to-person transmission, possibly by the fecal-oral route: The prevalence of *H pylori* is higher in persons from developing countries than in those from industrialized countries[22]; there is a higher prevalence than would ordinarily be expected in persons residing in long-term-care facilities[23]; there has been a report of a family in whom eight members have genetically identical strains of *H pylori,* suggesting person-to-person transmission[24]; and it has been shown that *H pylori* can survive in river water.[25]

The presence of *H pylori* can be determined by several different methods. First, *H pylori* can be seen on biopsy

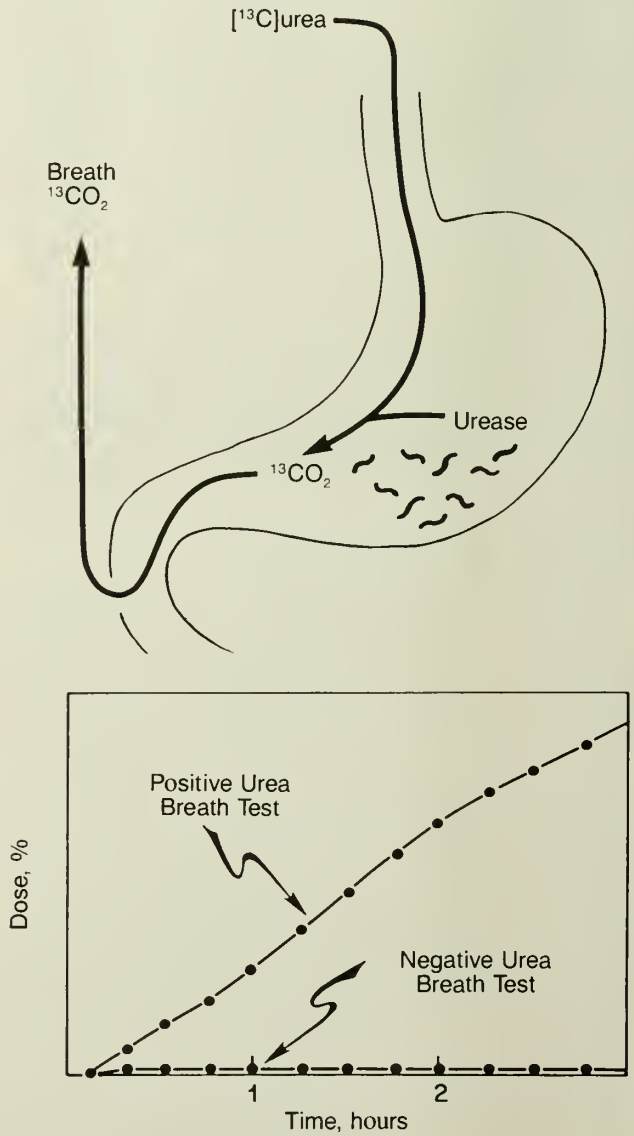

Figure 1.—The diagram and graph show the mechanism of the carbon 13-labeled urea breath test for detecting urease-producing organisms in the stomach. If ingested [^{13}C]urea degrades, producing $^{13}CO_2$, the test is considered positive for urease-producing organisms.

TABLE 1.—*Serum Antibodies to* Helicobacter pylori *Using an Enzyme-linked Immunosorbent Assay**

Antral Culture for H pylori	*Patients, No.*	*Optical Density Value*	
		IgA	*IgG*
Organisms present	29	1.26±0.08	1.71±0.07
Organisms not present	30	0.37±0.07	0.34±0.10

*Data expressed as the mean plus-minus the standard error of optical density (from Perez-Perez et al[29]). Differences are significant at $P<.00001$.

specimens of gastric epithelium using a number of tissue stains.[26] Experienced pathologists can often find the organism simply using the standard hematoxylin-eosin stain. The most sensitive special stain is the Warthin-Starry silver stain, but because this is a tedious and time-consuming technique, the use of the Giemsa stain is recommended when *H pylori* is not found with a hematoxylin-eosin stain. Second, *H pylori* can be cultured from tissue relatively easily now that the techniques have been perfected; and, third, the presence of urease can be detected either by pH-sensitive media or by a breath test, as an indirect means of finding *H pylori*.[27,28] With the breath test, urea is labeled with either carbon 13 or carbon 14 and ingested by the patient. If urease-containing organisms are present in the stomach, the labeled urea is degraded to produce $^{13}CO_2$ or $^{14}CO_2$, which can be detected in expired breath (Figure 1). The advantage of carbon 13 is that it is nonradioactive, but its disadvantage is that a mass spectrometer is needed for the determination. On the other hand, although carbon 14 is radioactive, its presence can be detected without expensive equipment. A final indirect test for *H pylori* is the determination in the blood of antibodies to the organism. Persons with *H pylori* determined by histologic examination, culture, or the urea breath test will almost invariably have high titers of immunoglobulin G and A antibodies to *H pylori* (Table 1).[29] Occasionally, however, a patient will have antibodies to *H pylori* but the organism will not be in the stomach. These antibodies undoubtedly reflect a previous infection with the organism in a person whose stomach has been cleared of the organism itself. One intriguing mystery surrounding *H pylori* is how it can elicit such a substantial antibody response and yet continue to flourish in its ecologic niche.

Numerous investigators have confirmed the close association between *H pylori* and histologically determined gastritis. In fact, when *H pylori* organisms are present in the antrum, gastritis is always found. The association is not so tight when the body mucosa is assessed. Here, in our experience, about 10% of patients with *H pylori* will have histologically normal mucosa. The association between *H pylori* and gastritis, however, does not prove a cause-and-effect relation. Unfortunately, there is no reliable animal model for *H pylori* gastritis. Two persons have, after their stomachs were rendered hypochlorhydric with an H_2-receptor antagonist, ingested large inocula of *H pylori*. In each instance, it was reported that gastric mucosa that had previously been normal became inflamed and now harbored *H pylori*. Beyond these two cases, the evidence to support *H pylori* as a pathogen causing gastritis is indirect, albeit persuasive. This evidence includes two observations. First, *H pylori* is seldom found in patients with gastritis of other known causes such as eosinophilic gastritis, Crohn's disease, or the atrophic gastritis associated with pernicious anemia. One explanation for the absence of *H pylori* in patients with pernicious anemia may

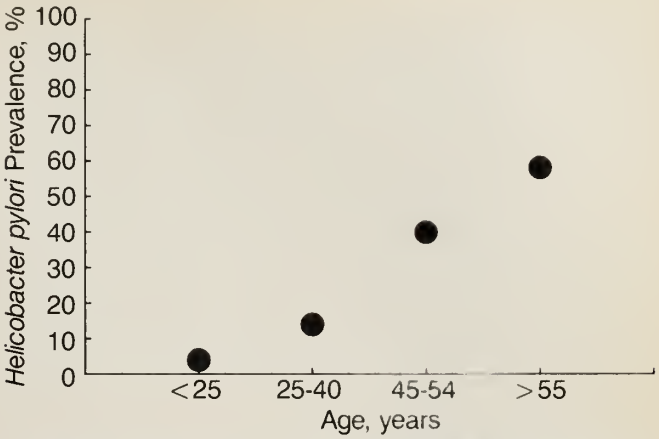

Figure 2.—The graph shows the prevalence of *Helicobacter pylori* in 73 asymptomatic healthy humans as determined either by histologic examination or by culture (W.L.P., unpublished observations).

be that such persons have extensive intestinal metaplasia, where *H pylori* is not found. Second, studies have now shown that eradicating *H pylori* with antimicrobial therapy is associated with an abatement or resolution of gastritis histologically.[30] It remains possible, however, that agents that eradicate *H pylori* may have some separate, intrinsic effect on mucosal inflammation. Further work with *H pylori* will be greatly enhanced by the development of either a convenient animal model or perhaps an ex vivo system using tissue culture techniques.

If it is accepted that *H pylori* does indeed produce an inflammatory response, the question remains, how does it do it? Preliminary studies suggest that *H pylori* may release a toxin that elicits an inflammatory response. Other studies suggest that ammonia produced from the metabolism of urea under the influence of urease may be cytotoxic. In one study using cultured gastric epithelium, administering acetohydroxamic acid, a urease inhibitor, reduced the degree of inflammatory response to *H pylori*.[31] Intensive efforts are being made to learn more about the pathogenicity of *H pylori* including such factors as its adherence to the mucosa and the elaboration of a toxin.

Helicobacter pylori gastritis is found in normal healthy persons. The prevalence in young persons tends to be low, but it increases linearly with age so that the prevalence of *H pylori* gastritis is high in healthy older subjects (Figure 2). There are several groups of patients in whom the prevalence of *H pylori* is higher than would be expected for a given age. Stated another way, these persons become colonized at an earlier age. For example, the prevalence of *H pylori* is higher at a given age in blacks and Hispanics than in whites.[32,33] Although this may be to some degree related to socioeconomic factors, it is possible that genetic factors also play a role. Patients with gastric and duodenal ulcer disease also have a higher prevalence of *H pylori* gastritis than do age-matched controls.[34] Finally, some studies suggest that patients with nonulcer dyspepsia have a higher prevalence of *H pylori* than normal, although other studies do not.

Because of the higher prevalence of *H pylori* in patients with various peptic diseases, it has been suggested that the organism may play a role in their pathogenesis. Again, because there is no animal model for *H pylori* gastritis-associated peptic ulcer disease, all evidence to support this association is indirect. Such evidence includes the following: First, patients with duodenal and gastric ulcer disease have a high

prevalence, at an early age, of *H pylori* gastritis[34]; second, it is thought that duodenal ulcers occur in areas of gastric metaplasia. Such tissue is frequently noted to be inflamed and to harbor *H pylori*; third, in two controlled trials recently it was suggested that eradicating *H pylori* leads to a prolonged remission in patients with duodenal ulcer disease.[35,36] In one of these studies, 35 patients with duodenal ulcer were treated and their ulcers healed with the use of bismuth subsalicylate alone or with bismuth subsalicylate plus an antibiotic.[36] Of 25 of those patients in whom *H pylori* was eradicated at the time of ulcer healing, ulcers recurred during the next 12 months in 6. On the other hand, 7 of 10 patients in whom *H pylori* was still present after therapy had an ulcer recurrence during the next 12 months.

While these data are provocative, several observations suggest that more evidence is required before the hypothesis is accepted. First, these studies were not well-blinded. Second, there is poor correlation when using "anti-*H pylori*" regimens between the eradication of the organism and ulcer healing, as opposed to ulcer recurrence. Moreover, an adequate number of patients has not been studied to prove that any salutary long-term effect of using bismuth with or without antibiotics is due to *H pylori* eradication rather than an intrinsic effect of the medications on gastroduodenal epithelium. Another factor is that agents that have no effect on *H pylori* (such as H_2 blockers, prostaglandins, sucralfate) heal ulcers effectively. In addition, in the stomach, *H pylori* gastritis is rather diffuse, yet ulcers are focal. Finally, it is well known that after healing, ulcers recur only periodically despite the fact that levels of gastric acidity remain relatively constant, as does the presence of *H pylori*. Thus, a role for *H pylori* in duodenal ulcer disease remains unproved. Even if *H pylori* proves to be a factor predisposing to the development of duodenal ulceration, it certainly is not the only factor. That is, although acid, and perhaps *H pylori*, are both necessary for the pathogenesis of duodenal ulceration, there are certainly other important factors.

Helicobacter pylori gastritis has also been suggested by some as a cause of nonulcer dyspepsia, but there are no convincing randomized, double-blind studies to suggest that symptoms of nonulcer dyspepsia are lessened more often with therapy directed toward *H pylori* than if a placebo is used. While it is possible that there may be a subset of patients with nonulcer dyspepsia whose symptoms are related to the presence of *H pylori* gastritis, this issue remains unclear.

The questions frequently arise whether *H pylori* should be treated, in whom, and how. At this stage of our knowledge, and until we have a much better grasp of the role of *H pylori* gastritis in disease, therapy should be limited to randomized controlled trials or to special circumstances. The latter include the two following situations. First are patients with nonulcer dyspepsia for whom all other forms of therapy have failed but who remain debilitatingly symptomatic. The other situation is patients with duodenal ulcer (but not Zollinger-Ellison syndrome) in whom medical therapy has failed but for whom surgical therapy is not desirable. It cannot be emphasized strongly enough that the treatment of *H pylori* in these patients is not based on scientific evidence of efficacy. Although such patients should, if possible, be entered into randomized controlled trials, the practical reality is that those trials are conducted in only a few centers, which is not much help to physicians with such patients in their practices. Therefore, until data confirm or refute the efficacy of antimicrobial therapy for *H pylori*, the following advice is offered: For patients with intractable nonulcer dyspepsia, an initial empiric course of bismuth subsalicylate is reasonable because the drug appears to be safe. In the United States, Pepto-Bismol,* two tablets four times a day for four weeks, can be tried. If this fails, and if an antral biopsy discloses *H pylori* gastritis, antibiotic therapy can be added for one to two weeks. Indeed, data strongly suggest that bismuth therapy alone results in long-term eradication in only about 25% of patients. An effective antibiotic regimen has not been firmly established, but it appears that adding metronidazole to bismuth therapy will produce an eradication in as many as 80% of patients. For patients with duodenal ulcer who would ordinarily be considered for surgical therapy but for whom the operative risk is high or they have refused, a trial of bismuth plus metronidazole may be warranted. Because of the possibility of bismuth intoxication if used long term, bismuth compounds should be used for only short periods of time.

Helicobacter pylori gastritis has provided an exciting new area of investigation into the pathogenesis of peptic ulcer disease. Many questions remain, however. We need to know more about how *H pylori* is transmitted, what its epidemiologic patterns are, why *H pylori* has a predilection for gastric and not intestinal epithelium, exactly how the organism elicits an inflammatory response, to what extent species variation from one strain of *H pylori* to another is important in terms of disease states, and what the role of *H pylori* is in disease states. An animal model or ex vivo system to study *H pylori* would be enormously helpful, and larger, more stringently designed, randomized controlled trials need to be done. Until these issues are addressed, physicians should view the importance of *H pylori* and its treatment with caution.

*Pepto-Bismol has not been approved by the US Food and Drug Administration for the treatment of duodenal ulcer.

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Epitomes

Important Advances in Clinical Medicine

Occupational Medicine

The Scientific Board of the California Medical Association presents the following inventory of items of progress in occupational medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in occupational medicine that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Occupational Medicine of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
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Electromagnetic Field Exposure and Risks of Cancer in Children

ALTHOUGH SIGNIFICANT strides have been made in the past two decades in the treatment of and survival from a few cancers of childhood, cancer remains the second leading cause of death in children younger than 15 years. Thus, interest in the etiology of childhood cancers, and particularly in potentially preventable exposures that might be associated with these cancers, has also grown.

One area of increasing investigation relating to environmental exposures associated with the risk of childhood cancer is that of electromagnetic fields—that is, the magnetic fields generated by flowing electric currents. One of the earliest studies, published in 1979, found an association of high-current-flow electrical wiring configurations near the homes of children in Colorado with about a twofold increased risk of childhood cancer deaths (all types grouped) compared with matched controls. A report from Rhode Island, however, indicated no such excess risk for childhood leukemia. In another study from Colorado in 1988, an excess of in-home wire configuration codes indicating high magnetic field (>2 milligauss) was associated with all childhood cancer and a number of specific types of cancer compared with that in control children. In addition, a study from Texas found a greater frequency of paternal occupations (electronics workers) involving exposure to electromagnetic fields among children who had died of neuroblastoma than among randomly selected, live-birth controls. A 1986 Swedish publication also showed increased magnetic fields (>0.3 microtesla) around the dwellings of children with tumors compared with those of matched control children.

Scientific investigations into any increased risk of childhood cancer associated with either parental occupational exposures or home exposure to high-current electromagnetic fields have been plagued by a variety of methodologic limitations. These particularly include inadequate or biased methods of exposure assessment due to occupational groupings that are too broad; exposure information missing for large proportions of the study population; a lack of uniformity across studies in the timing of the exposure of interest—that is, at birth of the child, at the time of the diagnosis of cancer in the child, or at the time of the study; and a dependence on parental (especially maternal) recall of paternal occupations or occupational exposures. In addition, the inconsistency of findings may be due to a variation in the nature of the cases included. Some studies have selected newly diagnosed cases, but many studies have identified cases from death certificates, even though most of the cancers in question are not uniformly fatal. In addition, some studies have examined all cancers together, while others have examined specific types, such as leukemia, brain tumors, or neuroblastoma.

An assessment of our current understanding of the effects of environmental exposures on the risk of childhood cancer with these methodologic concerns leads to a conclusion that paternal occupational exposure to high-current electromagnetic fields may increase the risk and is of interest due to the ubiquity of this exposure and suggestions in studies of animals of the potential for a cancer-promoting effect. Further well-designed studies, however, with adequate sample size and exposure assessment and including only incident cases of specific types of cancer are needed.

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Isocyanates, Polyurethane Paints, and Asthma

THE ISOCYANATES are important industrial chemicals used to make polyurethane plastics, which are common materials in our society. The cushioning for automobile seats and office and home furniture is usually polyurethane. Car bumpers are sometimes made of polyurethane. Polyurethane paints and coatings have found wide application in this country's economy because of their luster and resistance to weathering. All polyurethane paints contain diisocyanates or polyisocyanates, which are highly reactive low-molecular-weight compounds. The diisocyanate that previously was most commonly present in polyurethane products, toluene diisocyanate (TDI), has been the subject of extensive study in both laboratory and field studies.

The major adverse health effect associated with an occupational exposure to TDI is the induction of asthma. Al-

though the mechanism of TDI-induced asthma is unclear, its clinical presentation often suggests that "sensitization" occurs. Cases of hypersensitivity pneumonitis associated with TDI exposure also have been reported. Toluene diisocyanate is a mucosal irritant in higher concentrations, and workers who have had exposure to it who do not appear to be "sensitized" have had accelerated annual rates of decline in ventilatory function. Nonspecific airway hyperresponsiveness has been induced in guinea pigs after single, short-term exposures to TDI at a concentration of 3 parts per million, suggesting that immunologic sensitization is not the only etiologic factor.

Contrary to the usual conception of occupational asthma, a persistence of asthmatic symptoms and nonspecific airway hyperresponsiveness after exposure ceases appears to be the norm rather than the exception with TDI-induced asthma. Many studies have confirmed this alarming potential of TDI exposure. Because the duration of asthmatic symptoms before diagnosis is associated with persisting symptoms after the cessation of exposure, there is a need for prompt diagnosis and the removal of affected workers.

Because of the health risks associated with TDI exposure, other diisocyanate compounds have been used in the manufacture of polyurethane paints and coatings. In particular, hexamethylene diisocyanate is popular in automotive spray-painting applications. It is alleged by paint manufacturers that hexamethylene diisocyanate is a less potent asthma-inducer than TDI, but case reports of asthma and hypersensitivity pneumonitis induced by this compound make this questionable.

In an effort to reduce exposure to "free" diisocyanate monomers in spray painting, manufacturers have developed paints consisting primarily of polyisocyanates ("prepolymers"). Although measured diisocyanate exposure in spray-painting areas may be reduced by the use of prepolymerized paints, it is not clear that such paints are completely without asthma-inducing potential. Our experience is that cases of occupational asthma due to the use of prepolymerized polyurethane spray paints do occur.

It is prudent to advise employers to provide, and workers to wear, appropriate respiratory protective gear in polyurethane spray-painting areas even if diisocyanate levels have been measured to be below the threshold limit value. It is not at all clear that the current threshold limit value will prevent the development of asthma.

Clinicians can also participate in the solution of this problem by identifying one of the isocyanates as the cause of adult-onset asthma. The immediate removal of the affected person from the work setting is likely to be an important factor in the prognosis.

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Health Hazards of Occupational Diesel Exhaust Exposure

DIESEL ENGINES generate 50 to 100 times more particulates than do gasoline engines, and the organic extracts of diesel exhaust have been known since the 1950s to be carcinogenic in rodents. In the late 1970s the gasoline shortages and increasing number of light-duty diesel vehicles resulted in a heightened concern about the adverse health effects of diesel exhaust exposure. Since then numerous laboratory and epidemiologic studies have been completed addressing this issue.

Studies in the United States, Germany, and Japan have shown significant increases in lung tumors among rats with long-term exposure to high concentrations of diesel exhaust. Diesel exhaust carcinogenicity is both dose- and time-related. The mechanism of diesel carcinogenicity is thought to be the interaction of organic chemicals, particularly polycyclic aromatic hydrocarbons associated with diesel exhaust soot, with lung DNA. This is supported by recent studies showing higher levels of DNA adducts in the peripheral lung tissues of exposed rats, which is the location of diesel exhaust-induced lung tumors.

Diesel engines came into common industrial use in the 1940s and 1950s. Early epidemiologic studies were limited by inadequate latency times among exposed populations and poor estimates of diesel exposure. Many studies have also been limited by sample sizes too small to detect a small increase in lung cancer risk. Recent studies have addressed these limitations more adequately and have included populations with adequate sample sizes. An extensive series of studies among railroad workers in the United States found consistent evidence of a small but significant increase in lung cancer risk among current and former workers. For workers younger than 65 years with 20 years or more of exposure, the relative risk for lung cancer was approximately 1.3 to 1.4 compared with that of workers without such exposure. Studies among Canadian railroad workers and US truck drivers have had similar findings.

The laboratory and epidemiologic studies have resulted in the International Agency for Research on Cancer (IARC) recently concluding that there was sufficient evidence for carcinogenicity in animals of whole diesel engine exhaust and diesel engine exhaust particles. The IARC also concluded that there was limited evidence for carcinogenicity of diesel engine exhaust in humans. The risk from lifetime occupational exposure is small but biologically plausible and consistent with epidemiologic data. Populations at risk include persons whose occupations involve work in close proximity to operating diesel engines, such as railroad, bus, truck, and heavy equipment repair personnel and possibly operators. The data are limited on the possible interaction of diesel exhaust with other known lung carcinogens, including cigarette smoking.

There are few studies on the nonmalignant respiratory effects of occupational diesel exhaust exposure. Studies of miners have found an increase in some respiratory tract symptoms associated with diesel exhaust exposure, but no definite changes in pulmonary function have been found. Preliminary results of a mortality study have suggested that lifetime diesel exposure may be associated with increased

chronic obstructive pulmonary disease mortality. More work is needed on the possible nonmalignant effects of workplace exposure to diesel exhaust.

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Health Hazards of Radon Exposure

RADON, A CAUSE of lung cancer in miners of uranium and other underground minerals, has become recognized as a potentially important cause of lung cancer in the general population. This naturally occurring gaseous member of the uranium 238 decay series decays into a series of solid, short-lived isotopes referred to as radon daughters, progeny, or decay products. The release of α-particles by inhaled radon decay products is presumed to damage cells of the bronchial epithelium and thereby cause lung cancer.

As data on indoor air quality have accumulated, it has become apparent that radon and its decay products are present in indoor environments and at unacceptably high concentrations in some homes and other structures. Because the uranium-decay series is present in virtually all rocks and soils, radon contaminates the soil gas that passes into indoor and outdoor air. Thus in homes, the principal source of radon is the soil beneath the home, but building materials, water used in the home, and utility natural gas may also contribute. Measurements made in the United States indicate that the distribution of radon levels in houses is skewed, with the average at about 1.5 pCi per liter, but with many homes in the distribution's tail having much higher levels.

From animal and epidemiologic data, we have a sound understanding of some aspects of radon carcinogenesis. The lung cancer risk has been shown to increase with increasing exposure; the preponderance of the epidemiologic evidence indicates a synergism between cigarette smoking and radon exposure. The epidemiologic studies of underground miners provide the data needed to project the lung cancer risk of indoor exposure to radon. Computer models of the dosimetry of radon decay products in the lungs indicate a comparable potency of radon as a carcinogen with exposures in homes and in mines.

Although substantial uncertainty remains concerning the lung cancer risk associated with indoor radon, all projections indicate that the problem is substantial. Because carcinogenesis by radon is considered to follow a no-threshold exposure-response relation, any exposure, even the average for the population, conveys some risk. Remarkably high risks of lung cancer are projected for high exposures. For the US population, estimates of the annual number of lung cancer cases attributable to radon range from about 5,000 to 20,000 cases.

Health care providers should be prepared to advise patients concerning the risks of indoor radon and not dismiss the problem. Following the 1988 advisory of the Environmental Protection Agency (EPA), the measurement of radon in homes should be advocated. We lack other methods for identifying homes with unacceptable concentrations. Longer term measurements, rather than shorter term measurements with a charcoal canister, are preferred under most circumstances. The results of measurements should be interpreted cautiously, but mitigation should be advised for homes with high levels. The EPA's guidelines offer one framework for interpreting measurements, but the highest acceptable level—4 pCi per liter—is not a boundary between safe and unsafe levels. Smokers should be cautioned about the synergism between smoking and radon exposure and advised to stop smoking.

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Male Reproductive Toxicity

WORK-RELATED BIRTH DISORDERS are commonly regarded as related to the occupational experiences of pregnant women. Evidence suggests, however, that toxic exposures in men can also influence reproduction. There are many theoretic mechanisms by which this might occur: a pregnant woman might have direct exposure to a toxin inadvertently transported home from the workplace; a systemic, endocrine, or testicular toxic reaction could impair the male libido or fertility; and systemically absorbed chemicals that cross the blood-testis barrier or are secreted into seminal fluids might either damage sperm or directly affect a fetus or oocyte through sexual transmission.

A number of workplace chemicals have been reported to cause sperm abnormalities. Lead exposure, for example, has been shown in a study of 150 male storage battery workers to be dose-related to the prevalence of oligospermia, sperm hypomotility, and abnormal sperm characteristics. Exposures to boron, cadmium, manganese, and mercury have each been linked to sperm abnormalities, but these data come from small studies or case reports and are inconclusive. Abnormal spermatogenesis has also been described in epidemiologic studies of men with exposure to certain organic compounds, including carbon disulfide, chloroprene, dinitrotoluene and toluene diamine, and the pesticides carbaryl, chlordecone, and dibromochloropropane (DBCP). In many instances these sperm abnormalities have been of indeterminate clinical significance, but human exposures to lead and to DBCP have produced infertility, and the more severe cases of DBCP spermatotoxicity have been irreversible. There is generally minimal information from studies in humans or animals with which to judge the potential spermatotoxicity of the thousands of other commonly used industrial chemicals.

Many authorities question whether paternal chemical exposures can influence a partner's pregnancy outcome or cause abnormalities that are transmissible to offspring, but there is evidence that such adverse effects occur. Paternal exposures to lead, chloroprene, and DBCP have each been reported to increase rates of spontaneous abortion. Other epidemiologic studies have also suggested, for example, that partners of male anesthetists and of copper smelter workers are at risk for spontaneous fetal loss and that paternal "hydrocarbon" exposure may increase the occurrence of low birth weight, central nervous system malformations, and childhood cancers. Although few human studies have been confirmed with subsequent studies, they are supported in principle by the findings of animal research in which exposures of male animals to various alkylating agents have subsequently produced genetic mutations, chromosomal translo-

cations, malformations, and tumors detectable in first- and, in some studies, second-generation offspring.

There is a paucity of data regarding male reproductive toxicity, but the implications of the available data are broad. Workplace exposures should be considered in evaluating male infertility. Men attempting to start a family should be counseled to minimize chemical exposures. Finally, efforts to reduce workplace exposures to known or suspected reproductive toxins should be extended to both men and women.

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Ethylene Oxide Carcinogenicity

ETHYLENE OXIDE (C_2H_4O) is an important industrial chemical used in sterilization and many manufacturing processes. At ambient temperatures it is a gas. In vivo it is rapidly distributed throughout the body. Short- and long-term exposures may lead to respiratory irritation, central nervous system depression, and seizures. At high concentrations ethylene oxide can induce lethal mutations and is embryotoxic in animals. Ethylene oxide is able to alkylate DNA, causing gene mutations that lead to sister chromatid exchange abnormalities and chromosomal damage.

Ethylene oxide has been found carcinogenic in animals following subcutaneous, oral, and inhalation administration. Following oral administration, ethylene oxide produces an increase in local tumors, most notably squamous cell carcinoma of the forestomach in rats. Following inhalation ethylene oxide produces a substantial increase in the incidence of mononuclear cell leukemia in male and female rats and in that of peritoneal mesotheliomas in male rats. An increase in the incidence of brain tumors (rarely found in control animals) is also noted in male rats with exposure to ethylene oxide by inhalation.

Epidemiologic evidence shows an association between the exposure of humans to ethylene oxide and some forms of cancer. An excess of leukemia mortality has been reported in several epidemiologic studies, but these studies do not provide conclusive evidence for this association owing to the small number of workers studied and the possibility of exposure of the workers to other carcinogens. These studies, however, do provide some evidence for ethylene oxide's carcinogenicity in humans.

In 1985 the International Agency for Research on Cancer concluded that there is sufficient evidence for the carcinogenicity of ethylene oxide in animals and that the evidence of carcinogenicity in humans is limited. Overall, the review of this information suggests that the data on both animals and humans is sufficient to classify ethylene oxide as probably carcinogenic in humans.

In light of the importance of sterilizing medical equipment, especially with the danger of human immunodeficiency virus and hepatitis B infections, ethylene oxide will continue to be widely used. Human exposure to ethylene oxide should be kept as low as feasible given present-day technology. Health personnel working in close proximity to ethylene oxide should be given proper training as to ethylene oxide's dangers and be informed as to the known and uncertain risks of ethylene oxide exposure. The function of sterilizing equipment should be regularly assessed, proper ventilation established, and alarm systems installed.

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Occupational Back Pain of Nurses

HEALTH CARE WORKERS are potentially subject to a large number of occupational health hazards, ranging from carcinogens and mutagens such as ethylene oxide and chemotherapeutic agents to the effects of rotating shift assignments. Musculoskeletal disorders are also prominent among the problems faced by health care providers. Occupational back pain among nursing staff is common and leads to a considerable loss of valuable nurses. Epidemiologic studies in several countries—England, United States, Denmark, Israel—provide rather uniform estimates of the high frequency of such illnesses. An analysis of workers' compensation claims suggests that acute care hospital nurses are at risk and that nurses in chronic care facilities are at particularly high risk. For example, registered nurses are 5.1 times as likely to have back-related compensation claims as are cashiers, and nurses' aides are 22 times as likely.

In the past, much effort has been expended in training student nurses in the "proper-lift" technique to be used in patient transfers. There are several reasons why this has not succeeded in controlling the problem: First, the techniques taught may actually increase low-back stress. Second, other nursing activities besides lifting patients—such as moving equipment and standing in awkward positions for prolonged periods—may also be important in producing these problems. Third, such training may account for the attitude of many nurses that they are personally responsible for preventing their own health problems, thereby directing attention away from environmental factors. Fourth, many lifting assistance devices, such as the Hoyer lift, are awkward to use and so are underused. Fifth, hospital staffing patterns may not permit the use of two-person lifts. Sixth, understaffing and changes in work schedules, particularly the use of 12-hour shifts, may be exacerbating musculoskeletal work stresses. Finally, counting on workers to modify their work practices to decrease occupational injury and illness rates is generally less effective than appropriate environmental modifications. Successful intervention programs require a major commitment to providing help for individual nurses rather than providing "training" in groups.

Although back injury rates of nurses approach those of truckers and warehouse workers, nurses have a fundamentally different problem because they may risk injury to themselves in order to preserve and improve the health of their patients. In addition to continuing traditional proper-lift training and providing symptomatic treatment, it is important to encourage the proper reporting of nursing injuries, to encourage nurses to analyze their activities carefully, to apply well-known industrial ergonomic principles to hospital and hospital equipment design, and to consider carefully the

effects of scheduling and staffing changes. It is also essential to develop effective rehabilitation and limited-duty opportunities for nurses with back injuries. This mandate is particularly important in view of the increasingly severe nursing shortage; medicine can no longer afford the high attrition rates, absenteeism (often underreported), and impaired work performance caused by discomfort, medication use, or both. Back pain is solely responsible for 1.3% of those quitting nursing and was a "major" contribution to an additional 12% of those leaving.

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Occupational Liver Disease

ALTHOUGH A NUMBER OF industrial chemicals are known hepatotoxins, liver disease from occupational exposure is rarely suspected or diagnosed. Well-recognized hepatotoxins such as carbon tetrachloride, trinitrotoluene, and yellow phosphorus are no longer widely used, but numerous other organic solvents and chemicals that are known or suspected hepatotoxins are used extensively throughout industry. Several recent reports provide evidence that occupational liver injury may occur more frequently than is generally recognized. These reports help to both characterize occupational hepatotoxicity and suggest ways to distinguish it from other forms of liver disease.

An outbreak of liver disease among workers with routine exposure to a widely used solvent, dimethylformamide, was recently reported. After the index case presented with hepatitis, 35 of 46 of his co-workers (76%) were found to have elevated levels of liver aminotransferases, several more than tenfold. Although variably symptomatic, most of these workers had not sought medical attention. The alanine aminotransferase (ALT) level was higher than the aspartate aminotransferase (AST) level in all but one worker, a finding atypical for alcoholic liver disease. Evaluation of the workplace, a plant that produces polyurethane-coated fabrics, showed that large quantities of dimethylformamide, a known hepatotoxin, were being used in poorly ventilated areas and without appropriate skin protection. Most of the workers' aminotranferase values improved with removal from exposure, and no new cases have been detected since improvements were made in the workplace. Liver biopsy specimens from several of the workers showed histologic features consistent with a hepatotoxic injury. Findings included hepatocellular necrosis and microvesicular steatosis acutely and pronounced steatosis in those with more long-term exposure.

Other recent reports have documented hepatotoxic effects among workers with exposure to several different widely used solvents. Steatosis and elevated liver aminotransferase levels have been found among painters with exposure to various organic solvents. Similar findings were recently described among four workers with exposure to the solvent 1,1,1-trichloroethane. Fulminant hepatic necrosis after occupational exposure to 2-nitropropane has also been reported recently.

These studies suggest that occupationally induced liver injury does occur in modern industry, most commonly in workers with exposure to solvents, and that a high index of suspicion is necessary to make the diagnosis. The findings of elevated levels of aminotransferases, especially with the ALT higher than the AST, should alert clinicians to consider such a possibility. Necrosis or steatosis on a liver biopsy specimen, while nonspecific, is also suggestive of possible occupational liver injury. When other likely causes of liver disease—that is, viral and alcohol-induced—have been reasonably excluded, removal from potential hepatotoxic exposures should be seriously considered. The resolution of liver function abnormalities after removal from such exposures provides further support for an occupational origin. The natural history of mildly elevated aminotransferase values in the occupational setting is unclear, however, making it difficult to establish firm guidelines for removal. A strong suspicion of occupationally induced liver disease should prompt an industrial hygiene evaluation of the workplace and appropriate modifications of work practices, such as improved ventilation, appropriate protective clothing, and product substitution, to reduce potentially toxic exposures. Whether prolonged exposure to currently used hepatotoxic chemicals can cause chronic liver injury and cirrhosis is an important question that needs further study.

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Editorials

Memory and Amnesia

THE BIOLOGICAL FOUNDATION of memory functions is one of the most investigated and most productive areas of neuroscience. Recently the topic has benefited by convergent research in several scientific fields, such as cellular neurobiology, systems neuroanatomy, behavioral neurology, neuropsychology, and cognitive science.[1-6] In this issue of the journal, Erickson offers an interesting and informative overview of memory research as it relates to the analysis of amnestic disorders. No one article can provide an extensive review of the manifold issues and findings related to amnestic disorders; yet, the article does touch on many of the central topics currently at hand. In the following paragraphs, I highlight some of these central topics and address others that were not mentioned.

One of the most striking findings in the past decade has been the evidence of multiple memory systems in the brain.[4,5] A circumscribed amnestic disorder can occur in patients with bilateral damage to the medial temporal area (hippocampus, entorhinal cortex) or to the diencephalic midline (thalamic nuclei, mamillary nuclei). Anoxic-ischemic injury, viral encephalitis, Korsakoff's syndrome, and thalamic infarcts can produce a severe and rather selective memory disorder. Patients with these disorders exhibit impairment on neuropsychological tests of memory—such as tests of recall or recognition of a word list—despite normal intellectual and language abilities. Interestingly, amnestic patients can perform in an entirely normal fashion on certain "implicit" memory tests, such as tests of skill learning, classical conditioning, and priming.[7,8] For example, amnestic patients can learn to read mirror-reversed words and can retain the skill for as long as three months. Nevertheless, they exhibit no explicit or conscious knowledge of having read words before or even having previously seen the testing apparatus.[9] These findings suggest that there are multiple forms of memory, such that certain forms can be preserved even when there is damage to the memory system involved in conscious memory for facts and episodes. These preserved memory functions have been described as habitual, skill-based, procedural, or unconscious forms of memory.[4-9] In addition to providing insights concerning the neural basis of memory, these findings also facilitate the development of rehabilitative and pharmacological interventions.

One issue of memory research that deserved more attention in the review by Erickson is the advancement in neurobehavioral analyses of nonhuman primate models of amnesia.[4,5] Recent progress in this area has occurred as a result of more appropriate behavioral tests and better lesioning techniques. Earlier the field was fraught with inconsistent findings, and it was thought that animal models of memory were inadequate. Recently, however, it has been shown that inconsistent findings were due to the fact that the behavioral tests were not specified clearly. In the past, any test of "memory" was deemed relevant because researchers were unaware of the notion of multiple forms of memory. Now it is understood that some forms of memory function are actually spared in animal models of amnesia, just as they are spared in clinical cases. For example, monkeys with medial temporal lesions exhibit impairment on memory tests such as the delayed, nonmatching-to-sample test, a test in which the monkey must remember which of two toy objects was rewarded. Yet, these lesioned monkeys exhibit normal performance on certain skill-based tests.[10] Animal models have advanced our understanding of the neural systems critical for memory. For example, studies using monkey models have recently shown that neocortical areas surrounding the hippocampus—such as the entorhinal cortex, perirhinal cortex, and parahippocampal gyrus—themselves play an important role in memory formation.[10]

Advances in scientific knowledge are often preceded by advances in technology. Such is the case in the investigation of the neuroanatomy of memory. Newly developed neuroanatomic tracing techniques[1] and in vivo imaging techniques[11,12] have provided important data concerning the neural tissue involved in memory. For example, recent studies of cortical pathways have shown that the medial temporal area projects to and receives projections from many polymodal areas in cortex.[1] In vivo imaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography have strengthened our understanding of structure-function relationships. In fact, a newly devised protocol for MRI scans has identified hippocampal damage in amnestic patients.[12]

One exciting area of memory research that was described by Erickson is the role of *N*-methyl-D-aspartate (NMDA) receptors in the formation of long-term potentiation. The biophysics of NMDA receptors is well suited for associating contemporaneous activity from multiple inputs. These receptors are most concentrated in the hippocampus, though they also occur elsewhere in cortical and subcortical areas.[13] Interestingly, the blockage of NMDA receptors eliminates the formation of long-term potentiation and also impairs learning and memory performance in rats.[14,15] What was not described by Erickson is that the mechanism of NMDA receptors provides a useful way to construct neural network computational analyses of memory systems.[16,17] Neural network theories have only begun to be used in analyses of memory formation, and progress in this kind of analysis will certainly advance the field.

Finally, the role of frontal lobe damage to amnestic disorders is a topic that has become a central issue in amnesia research.[18,19] Certain causes of amnesia, such as Korsakoff's syndrome and viral encephalitis, as well as dementing diseases such as Alzheimer's disease and Pick's disease can produce damage to the prefrontal cortex. Recent findings suggest that patients with circumscribed frontal lobe lesions do not exhibit gross memory impairment on standard clinical tests of memory. Yet they do appear to have a qualitatively different kind of memory impairment. Patients with frontal lobe lesions exhibit impairment on tests of temporal order memory—tests that ask subjects to determine which of two stimuli occurred more recently. Such patients also exhibit source amnesia—that is, they remember certain facts but forget when and where they were encountered.[19] In addition to these deficits, which are often referred to as "impairments of temporal context," patients with frontal lobe lesions also exhibit poor metamemory—that is, they have difficulty judging what they know and often do not plan and initiate memory strategies.[19] Analyses of the kinds of amnestic dis-

orders associated with damage to prefrontal cortex have only just begun. Further studies will certainly illuminate how this area contributes to memory function.

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Occupational and Environmental Illness and the Poison Center

WITH THE PUBLICATION OF THE ARTICLE by Blanc and coworkers in this issue of THE WESTERN JOURNAL OF MEDICINE, the literature now contains the complete cycle of this group's work analyzing occupational exposures reported to regional poison centers.[1,2] As such, their work deserves the scrutiny of all occupational physicians, toxicologists, and relevant government agencies with toxicologic responsibilities in the occupational, environmental, and health arenas. Compelling evidence is presented to confirm the inadequacy of current reporting systems for occupational exposures. Moreover, these studies highlight the disparity between increasing exposures, public awareness, and health professional inquiries and the paucity of institutions and trained specialists to provide knowledgeable counsel and care. Taken together, these findings have substantial medical, occupational, political, and public health import.

Among the nearly half a million physicians in the United States today, only 1,378 have been certified in occupational medicine since 1955 (even in 1988, only 121 physicians were newly certified [American Board of Preventive Medicine, Dayton, Ohio, written communication, September 1989]), and fewer than 125 are certified in medical toxicology (only 15 in 1988).[3,4] Moreover, only a handful are certified in both disciplines, and there are no formally recognized training or certifying procedures in environmental medicine. Data from the American Association of Poison Control Centers (AAPCC) indicate there are at least 86,000 occupational exposures to toxic substances each year in this country. (The AAPCC National Data Collection System documented 25,368 occupational exposure cases in 1988 from 63% of the US population.[5] In 1988 AAPCC used an extrapolation factor of 3.4 to estimate actual exposures compared to the 1,368,748 total reported exposures.) This may considerably underestimate occupational exposures due to a relative lack of awareness of poison centers' ability to assist in this area. Such a postulate is strongly supported by the magnitude of occupational illness in the United States, with estimates of the incidence of occupational illnesses and injuries ranging as high as 12 million cases per year.[6] The incidence of exposure to chemical hazards has doubtlessly risen in our increasingly technological civilization, yet considerable but heretofore-occult occupational illness is likely surfacing in response to a promulgation of exposure standards, right-to-know legislation, and media-induced "toxic terror." The entire situation has attracted the formal attention of the National Academy of Science's Institute of Medicine and the National Research Council. These organizations have expressed profound concern over the shortage of trained physicians and resources to handle the growing number of occupational exposures and illnesses.[7]

Few would dispute that occupational and environmental illnesses are widely underestimated and underreported, and Blanc and coauthors have demonstrated this phenomenon within the subset of occupational exposures. Using indirect and direct comparisons with extant reporting systems, they have found that the traditional and established reporting systems failed to capture 68% to 92% of occupational exposure cases—particularly clinically serious cases—reported to the regional poison center.[2] This is especially remarkable as California, the site of the study, has perhaps the most extensive array of occupational and environmental exposure reporting systems of any state. Unquestionably there is a manifest role for the AAPCC-certified regional poison centers to supplement and validate current occupational illness reporting systems.

According to the studies of Blanc and associates, patients concerned about occupational or environmental exposures will seek assistance from some combination of public health agencies, primary care physicians, the company or employer's physician, and poison centers. This fragmentation induces confusion and poses problems with the reporting, consultation, and follow-up of these patients. Ultimately, all exposures are fundamentally a medical problem with economic, occupational, and legal components; yet, the number of trained occupational physicians and medical toxicologists is clearly inadequate to address this need. Company physicians are perceived as insufficiently independent to serve as objective patient advocates, and primary care physicians are not trained to handle these problems. (The average US medical student will receive less than three hours of instruction in these areas over the four-year curriculum, and the vast ma-

jority of primary care residency programs—internal, family, and emergency medicine—offer no formal experience in these areas.[7]) Public health agencies are understandably not oriented to interact with patients in a comprehensive, consistent, or individual manner. Where are these patients and their physicians to turn? Increasingly, it seems, it is to the regional poison center.

Over the past five years the percentage of reports to poison centers of exposure that is occupational has nearly doubled, rising from 2,445 cases (0.97% of exposure consultations) in 1983[8] to 25,368 cases (1.85% in 1988),[5] despite the fact that poison centers still focus on acute overdoses of pharmaceuticals and pediatric ingestions of household products, rather than adult occupational and environmental exposures in subacute and chronic circumstances. Nevertheless, because of their toxicologic expertise, information resources, concentrated experience, and awareness of prevention and treatment programs, regional poison centers are a compelling venue to orchestrate the provision of counseling, medical care, and exposure-site investigation of these cases. Patients, physicians, and governmental agencies have grown to trust regional poison centers to provide timely, knowledgeable advice with flexible, readily accessible human services—free phone calls, anonymity when requested, no user fees—and a full range of expert backup. Furthermore, health professionals appreciate that computerized access to informational data bases alone is inadequate, and they have come to depend, instead, on a poison center's ability to provide not only relevant information but also the interpretation and application of that information to specific clinical scenarios. Over the past decade, regional poison centers have become highly professional, sophisticated, and computerized operations, with extensive on-line resources, specialized toxicologic expertise, public and professional education programs, and consultation provided by trained and certified specialists in poison information and by clinical toxicologists. These established relations and familiarity with regional considerations—industry, location, climate, economics, and politics—often prove essential in dealing with an occupational exposure and illness.

From a public health standpoint, regional poison centers have a proven data collection system able to accommodate a substantial increase in the number of occupational and environmental exposures. Adaptations of this AAPCC National Data Collection System would allow poison centers to provide ongoing surveillance with singular active attributes—education, management, referral, and follow-up. Moreover, poison centers are likely sources of information regarding index cases of affected or exposed workers, and these sentinel cases can be of utmost importance in identifying multiple exposures, discovering the source, and initiating remediation—all in cooperation with local public health agencies. (Indeed, Bresnitz has found that such reports to regional poison control centers represent only the tip of the iceberg, with, on average, 12 additional workers being exposed for every inquiry or report [E. A. Bresnitz, "The Evaluation of Poison Control Centers as Surveillance Systems for Occupational Illness," unpublished data, 1989].) The regional poison center model has not only been embraced by the public, physicians, and government, it has had a highly cost-effective impact[9,10] on the use of medical resources while at the same time providing state-of-the-art guidance that likely leads to decreased morbidity and mortality. Finally, perhaps the most enduring public health effect regional poison centers could have would be in the areas of education, informational data-base development, and research. Obviously, each inquiry or report is fundamentally an educational encounter for the caller, but regional poison centers can also be instrumental in promoting professional education for physicians, nurses, and pharmacists; training clinical toxicologists; developing useful resources; and stimulating research in this field.

Regional poison centers already participate in the management of a significant (and apparently otherwise unrecognized) burden of occupational or environmental illness. They are uniquely able to provide an active surveillance system to supplement current reporting systems, guide the care, counseling, referral, and follow-up of patients, help educate the public and primary care physicians, assist employers and industries to contain and avoid toxic exposures, and encourage scientific and epidemiologic investigations of occupational and environmental exposures and illness. These capabilities expressly meet the agenda laid out in the recommendations of the Institute of Medicine report on occupational and environmental medicine.[7]

Regional poison centers have a unique potential to evolve a system for the reporting, care, education, and research in environmental and occupational exposures. Logistically, however, these centers are not in a position to seriously expand into this field without the necessary financial and personnel resources. If these poison centers are to become broad-based toxicology resource centers, each center will have to expand its activities. Expertise in industrial hygiene and occupational and environmental toxicology needs to be brought on board. Current staffs need to be trained in these specialized areas. Operational protocols and comprehensive yet concise informational data bases need to be developed. National and local experts, response systems, and resources must be identified and combined into a network. Working protocols and relations with local, state, and federal agencies must be developed. Existing data collection systems must be expanded to active surveillance and ready detection of sentinel health events. Finally, the public, health professionals, and the work force need to be educated to an expanded role of regional poison centers as they become true toxicologic resource centers.

State health departments and agencies with mandates in this field—the Agency for Toxic Substances and Disease Registry, the Environmental Protection Agency, the National Institute of Environmental Health Sciences, the National Institute for Occupational Safety and Health, and the Occupational Safety and Health Administration—need to cooperate with and encourage the regional poison centers and the AAPCC during this evolution. The opportunity to deal with occupational and environmental exposures in a coordinated, comprehensive, and capable manner through regional poison centers needs to be supported if the promise of regional poison and toxicology resource centers is to materialize.

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On Rocks and Hard Places

During their training, physicians study human biology and come to a degree of understanding of the human mind and body within the framework of biologic law in the natural world. There has been enormous progress in our degree of understanding, and, indeed, bioscience has been the foundation upon which modern medicine has been built. As this understanding has increased and the technology to apply it has advanced, medical care has become much more complex and costly, with results, to be sure, that are often spectacular. As interest in health and health care has grown, much of the new knowledge and technology has entered into the public consciousness, if not the public domain. This public interest has been intensified by concern and even alarm over rapidly rising costs. Because of this, third parties who pay the bills in both the public and private sectors have become increasingly involved in many aspects of health care delivery. A turning point that began the present era was passage of the Medicare law in 1965, and third party involvement in patient care has been progressing ever since.

With the entry of these third parties, new expectations were introduced into patient care and health care delivery. Whereas physicians, by reason of their training, considered medical practice and patient care in terms of their understanding of biologic laws of nature as applied to health and illness, this was not so much the case with the new third parties, whose motives were based largely, though certainly not entirely, on their concern with economic realities. They soon began to introduce and apply the business and legal expertise of society to health care by fostering economic competition, enacting legislation to try to control costs, introducing administrative regulation, and indulging in litigation.

So it comes about that there are now two standards or systems at work in health care that are in fundamental conflict. The biologic system is one created by nature and operates with its own natural laws. These are expressed in terms of probabilities, and these probabilities are always accompanied by possibilities that are more or less probable but nevertheless equally real. Much of what is done in medical practice is determined by a physician's assessment of the probabilities and possibilities inherent in a given situation. This biologic fact of life is not readily recognized by the legal system. Laws created by society are artificial rather than natural. Yet they must be respected and obeyed in a human society governed by law.

The differences come into focus especially when there is a medical injury accompanied by litigation. The legal system assumes that the injury should not have happened, but since it did, it seeks to affix blame and punishment and to give compensation to the aggrieved party. The trial is public, conducted with attorneys for the plaintiff and defendant jousting with one another in court, using their wits and knowledge of the rules of law created by humans as their weapons. The facts of the case are sought but used selectively as deemed best for the cause of prosecution or defense. Right or wrong is decided in light of whether or not there is compliance with more or less arbitrary rules established through legislation or by the courts. It is seldom recognized that guilt or innocence may exist in terms of the probabilities inherent in the biologic law that governs patient care.

The biologic approach to an unfortunate medical happening is quite different. The approach is "no-fault." True to bioscience, it tries to get at the full truth of what really happened and why it happened and then to use this information positively with the view of gaining experience and preventing an unfortunate event from being repeated. The focus is on getting to the truth, wherever it may lie, but if there was genuine wrongdoing, it is understood that whatever blame, punishment, and compensation are appropriate should be meted out.

The art and science of medicine clearly lie within the realm of biologic law, but practice must respond to legal as well as biologic standards. Physicians in daily practice cannot escape either rule. Their patients are governed by biologic law in their sickness and their health. Medical practice is increasingly governed by societal law and regulation. It is not surprising that physicians sometimes find themselves between rocks and hard places when the two systems conflict, as is often evident when a medical practice issue involving an untoward outcome is being adjudicated in the courts. But there may be a ray of hope. It was only during the last century that the fundamentally biologic nature of humans was finally recognized. The inescapable consequence—that human society itself is therefore fundamentally biologic in nature and behavior and subject to biologic law—has yet to be similarly recognized. Progress is slow, but sooner or later there has to be light at the end of the tunnel. In the meantime there will be many rocks and many hard places in a physician's practice.

MSMW

Public Health and Preventive Medicine

Occupational Illness and Poison Control Centers
Referral Patterns and Service Needs

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This is one of a series of articles from western state public health departments.

In a study of occupational illness reported to a regional poison control center and to gauge the center's outreach and services, we did follow-up interviews of 301 case contacts over a 6-month period. We ascertained referral routes, reasons for contacting the poison control center, and awareness of the center's function. For 122 cases a nonphysician was the initial poison control center contact. Of the nonphysician contacts, 41 had already consulted a health care provider and been referred to the poison control center for assistance. Of the 70 persons with exposure, only 21 had been aware before their exposures that poison control center services might include occupational chemical illness consultation. Physicians and nonphysicians expressed similar reasons for contacting the poison control center, with 118 of 301 identifying the need for an exposure hazard risk assessment. These data suggest that although those contacting a poison control center because of occupational illness include a variety of cases, they have many similar service needs.

(Blanc PD, Maizlish N, Hiatt P, et al: Occupational illness and poison control centers—Referral patterns and service needs. West J Med 1990 Feb; 152:181-184)

In a retrospective study of case detection of occupational illness through a regional poison control center, we suggested that occupational illness reporting is an important and growing part of poison control center activities.[1] The American Association of Poison Control Centers recorded more than 21,000 occupationally related exposure cases in 1987.[2] Other investigators have also focused on the role of poison control centers in occupational health.[3,4] The Institute of Medicine has also recognized the importance of poison control centers in the treatment of occupational illness.[5]

We have recently reported results of a prospective study of occupational illness reported to the San Francisco Bay Area Regional Poison Control Center.[6] That study included follow-up interviews with those contacting the poison control center, which were carried out to obtain further information on exposure and treatment. We present here interview responses concerning poison control center referral patterns, motivation in contacting the poison control center, and awareness of poison control center services. We studied these questionnaire responses with the thought that they might clarify the ways in which these occupational cases came to the attention of the poison control center and the kinds of interventions those contacting the poison control center were seeking. Such information could assist the poison control center in planning effective outreach and services for the future.

Methods

We studied all cases reported to the San Francisco Bay Area Regional Poison Control Center logged in telephone consultations from July 1 to December 31, 1986. We used the following study entry criteria: cases originating in California; poison control center staff coding of the initial consultation according to American Association of Poison Control Centers criteria as occupational, symptomatic, and with stated symptoms possibly related to the recorded exposure. We did not study asymptomatic cases, limiting study to those with symptomatic exposures in order to study a group with potentially serious exposure.

As a part of the poison control center's quality control activities, we contacted each exposed person ("exposure case"); treating health care provider, if direct medical examination took place because of the reported exposure ("physician contact": this category may also include nurse practi-

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tioners or physicians' assistants); and "third-party" poison control center callers, if such contact took place. Treating physician contacts entered the study each time they treated an exposure case. We carried out follow-up two to six weeks after the initial poison control center consultation. A detailed description of case selection, study methods, and survey response rates has been presented elsewhere.[5]

We completed five- to ten-minute structured telephone follow-up interviews with all exposure cases, physician contacts, and third-party contacts. As a part of those interviews, we asked a series of questions regarding past contact and familiarity with poison control centers, the route of referral, and motivating factors in seeking a poison control center consultation. In regard to awareness of the poison control center, exposure cases and third-party callers were asked, "Before this illness or injury, had you been aware of a 'poison control center' that doctors or the public could call for information about toxic chemicals?" and, if yes, "Before this illness or injury, were you aware that poison control centers could assist in cases of adults with problems that might be due to chemical exposures on the job?"

All those surveyed were asked in an open-ended question, "What would you describe as your major reasons for contacting the San Francisco Bay Area Regional Poison Control Center?" As many as three responses were recorded. Because these responses were open-ended, we reviewed them after all the interviews had been completed and coded them into general categories of service need, such as "hazard risk assessment," "exposure identification," or "treatment advice." Because all the exposure cases included in this study were symptomatic, the category of "hazard risk assessment" included many respondents who wished to ascertain whether the symptoms experienced represented a substantial health risk, particularly with regard to possible long-term sequelae. In contrast, the "treatment advice" category reflects those seeking guidance in specific first-aid or medical interventions such as decontamination or administering an antidote.

Data were entered and edited in computer files. Differences between exposure case callers and third-party callers were tested with the χ^2 analysis or Fisher's exact test.

Results

Among 122 cases of symptomatic occupational exposure reported to the poison control center by nonphysician contacts, the exposure case was the contact in 70 cases (57%; 95% confidence interval [CI], 48% to 66%), and a third party was the contact in 52 (43%; 95% CI, 34% to 52%). The distribution of the 52 third-party poison control center contacts was as follows: 21 callers (40%; 95% CI, 27% to 53%) were co-workers of the exposure case, 11 of whom had a workplace supervisory role; 15 (29%; 95% CI, 17% to 41%) were family members or nonworkplace friends of the person with exposure; and for 16 (31%; 95% CI, 18% to 44%) there was some other or unstated relationship to the exposure case. This last group included contacts from nonphysician health care workers outside the workplace, such as "advice nurses" carrying out telephone consultations.

Table 1 presents follow-up questionnaire responses related to referral patterns among the exposure case callers compared with third-party callers. In both groups, a majority of callers had contacted a poison control center for the first time as a result of the reported occupational exposure. Overall, 34 (28%) had contacted a poison control center previously, but in only a few cases had this been specifically for an occupational exposure. The source of referral was similar in both groups. About a third were self-referred. Another one of three callers had already contacted a physician or health center and been referred to the poison control center through this source. The workplace was an uncommon route of referral, such as through an on-the-job emergency response protocol or the advice of work-site safety and health personnel.

The motivation for referral was also generally similar among both exposure cases and third-party callers. Most stated that they had sought an assessment from the poison control center of the degree of hazard to which they were exposed or wished specific first-aid advice. The need for chemical or product identification, although less frequent in both groups, was significantly more common as a motivating factor among the third-party callers compared with the exposure cases ($P < .05$). Advice on the need for physician referral was infrequently stated by either group as a factor in consulting with the poison control center.

TABLE 1.—*Referral Patterns for Nonphysician Poison Control Center Contacts (N=122)*

	Type of Poison Control Center Contact			
	Exposure Case		Third Party	
Referral Pattern	*No. (%)*	*95% CI, %*	*No. (%)*	*95% CI, %*
All nonphysician contacts	70 (100)	...	52 (100)	...
Previous center contact	17 (24)	14 to 34	17 (33)	20 to 36
Occupational exposure	4 (6)	1 to 11	6 (12)	3 to 21
Other exposure or ingestion	13 (19)	10 to 28	11 (21)	10 to 32
Source of referral				
Self	24 (34)	23 to 45	18 (35)	22 to 48
Health care center	23 (33)	22 to 44	18 (35)	22 to 48
Workplace	4 (6)	1 to 11	8 (15)	5 to 25
Other or unknown	19 (27)	17 to 38	8 (15)	5 to 25
Reasons for contact*				
Exposure identification	3 (4)	0 to 9	10 (19)	8 to 30
Hazard risk assessment	33 (47)	35 to 59	17 (33)	20 to 46
First-aid information	20 (29)	18 to 40	22 (42)	29 to 55
Referral to physician	6 (9)	2 to 16	4 (8)	1 to 15

CI=confidence interval

*Multiple responses possible.

TABLE 2.—*Awareness of Poison Control Center Among Nonphysician Contacts*

	Poison Control Center Contact			
	Exposure Case		Third Party	
Source and Degree of Awareness	*No. (%)*	*95% CI, %*	*No. (%)*	*95% CI, %*
Previously aware of poison center	48 (100)	...	33 (100)	...
Aware of occupational services	21 (44)	30 to 58	30 (91)	81 to 100
Source of awareness of center*				
Television or radio	17 (35)	22 to 48	4 (12)	1 to 23
Other public information	14 (29)	16 to 42	10 (30)	14 to 46
Health care provider	9 (19)	8 to 30	18 (54)	38 to 72
Workplace	8 (17)	6 to 28	13 (39)	23 to 57
Family or friends	12 (25)	13 to 37	1 (3)	0 to 9

CI=confidence interval

*Multiple responses possible.

TABLE 3.—*Physician Contacts to Poison Control Center for Cases of Occupational Exposure*

Physician Response Pattern	Physician Contacts No. (%)	Physician Contacts 95% CI, %
All physician contacts	179 (100)	...
Previous center contact	168 (94)	91 to 97
Occupational exposure	132 (74)	68 to 80
Other exposure or ingestion	36 (20)	14 to 26
Reasons for contacting poison control*		
Exposure identification	37 (21)	15 to 27
Health hazard assessment	68 (38)	31 to 45
Treatment information	69 (38)	31 to 45
Medicolegal considerations	5 (3)	1 to 5

CI=confidence interval

*Multiple responses possible.

Of the 72 exposure-case callers, 48 (67%; 95% CI, 58% to 76%) were aware of the existence of poison control centers previous to this exposure. Similarly, 33 of 52 (63%; 95% CI, 52% to 74%) third-party callers were generally aware of poison control centers. Table 2 summarizes questionnaire responses concerning an awareness of poison control center services among the exposure cases and third-party callers. The source of poison control center awareness was different between the groups. Television or radio and family or friends were both significantly more frequent routes by which exposure case contacts had become aware of poison control centers compared with third-party callers ($P<.05$). In contrast, health care providers or the workplace were the most frequent routes by which the third-party contacts had become aware of poison control centers, both routes being significantly more common than among the exposure cases ($P<.05$). Only poison control center awareness from nonbroadcast public information sources, such as telephone directories or telephone stickers, was similar in both groups.

When asked about occupational exposure consultations, only 21 of the 48 exposure cases (44%; 95% CI, 30% to 58%) generally familiar with the existence of poison control centers said that they had been aware that this was a possible service of the poison control center. These 21 cases constituted 30% (95% CI, 20% to 40%) of all the exposure-case contacts. In contrast, among third-party callers, 30 (91%; 95% CI, 60% to 100%) of the 33 cases familiar with the poison control center responded that they had been aware that the poison control center could offer occupational exposure information. These 30 cases represented 58% (95% CI, 45% to 71%) of all third-party callers. This difference between exposure case and third-party contacts was statistically significant ($P<.001$).

As shown in Table 3, of 179 cases of occupational exposure in which physicians were the initial poison control center contact, most had previously consulted the poison control center about another occupational exposure case. Most others had previously contacted the poison control center for a nonoccupational consultation. The physicians' most commonly stated motivations for contacting the poison control center were the need for toxicity hazard assessment or for specific treatment recommendations. Product content identification was cited as a specific consultation need by 37 physicians (21%; 95% CI, 15% to 27%). Medicolegal considerations were an infrequent motivating factor for the physician contacts.

Discussion

Although data derived from standard poison control logs have been available for review, previous poison control center occupational studies have not been based on structured follow-up interviews with both physician and nonphysician contacts.[1] The study design we have used provides the opportunity to additionally evaluate the poison control center from the point of view of those using its services.

Poison control centers are an unusual type of health care provider because they serve both health care professionals and the lay public. We have analyzed a deliberately narrow spectrum of poison control center consultations: symptomatic occupational exposures. These data show that persons contacting the poison control center even for this specific indication represent a diverse group when defined by type of caller, source of referral, consultation need, or awareness of services.

Many of the persons with exposure and third-party callers contacted the poison control center by an unexpected referral route: other health care providers who had recommended they consult with the poison control center. In other words, rather than directly evaluating the person with exposure and then contacting the poison control center for guidance (which would have constituted a physician contact), health care providers deferred to an independent poison control center intervention. One reason for this may be physicians' and nurses' unfamiliarity with toxic exposure effects and management. This is supported by the frequency with which the need for toxicity information and symptom evaluation was stated as a service need among both physician and nonphysician contacts. In contrast to the case with health care providers, the infrequency with which the workplace was a source of nonphysician case referral suggests that on-the-job safety protocols that include contacting a poison control center are not widespread. An occupational telephone hot line managed by the California Department of Health Services reported a similar infrequency in workplace-initiated referrals, although their data included both symptomatic and asymptomatic callers.[7]

Our findings also indicate that although general awareness of poison control center services is widespread, it is far from universal among the lay public. Moreover, most persons with exposure had been unaware that the poison control center treated occupational chemical illnesses until their symptomatic exposure occurred. These responses suggest that expanded public health education about poison control center services is needed, particularly targeting information sources such as the workplace that have not as yet been effectively exploited.

As would be expected, most of the physician contacts were familiar with poison control center services. Yet, their reasons for seeking an occupational consultation once again reflect uncertainty and the need for hazard information. Physicians are frequently unsure if any treatment is indicated or what exactly the exposure in question was. Despite the potential of Workers' Compensation claims or product liability issues, medicolegal concerns are not currently a prominent motivating factor for physicians contacting a poison control center.

Taken together, these findings support the view that poison control center consultations for occupational exposures provide hazard assessments for which both health care

providers and the lay public feel a need. As awareness of this poison control function increases, these services will likely be used even more frequently. To meet this challenge, poison control centers will have to direct staff training and educational resources to assure an adequate occupational health component to their services.

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Book Review

The Western Journal of Medicine does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.

Intensive Care—Facing the Critical Choices

Thomas A. Raffin, MD, Associate Professor and Assistant Chief of Medicine and Associate Director of the intensive care units, Stanford University Medical Center; Joel N. Shurkin, science writer, Stanford University News and Publications Service; and Wharton Sinkler III, MD, anesthesiologist and Episcopalian minister. W. H. Freeman and Company, 41 Madison Ave, New York, NY 10010, 1988. 204 pages, $14.95.

Intensive care unit experiences are often agonizing for both patients and families. The threat of serious illness may be compounded by an unfamiliar setting and by complex, challenging questions. *Intensive Care* was written to help prepare readers "for the possibility of facing critical choices in the Intensive Care Unit." The authors, a critical care physician, an anesthesiologist who is also a minister, and a Pulitzer prize-winning science writer, effectively use their diverse backgrounds to provide an informative, accessible guide to the intensive care unit.

Case reports are employed to introduce readers to the anatomy, physiology, and pathophysiology of major organ systems, including the heart, lungs, kidneys, liver, brain, and central nervous system. The authors' fundamental approach to dealing with disturbed function of these systems is "to save the salvageable by restoring health and help the dying to a peaceful and dignified death." Interesting insights into improving a patient's general health in the intensive care unit through exercise, nutrition, rest, and personal encouragement are described.

Chapters dealing with death, ethics, law, and economics are especially well-written and instructive. Fundamental ethical principles are stated. The practical and sometimes conflicting application of these principles is discussed with reference to specific questions such as initiation of basic life-support measures and withdrawal from extraordinary life support. The authors correctly emphasize that patients "have a right to govern what happens to their own bodies." Many readers will be surprised to learn that the basic cost of intensive unit care is $2,000 to $3,000 per day. The authors discuss these costs in terms of morbidity and mortality and candidly raise the inevitable question of rationing care. They also emphasize that additional data are necessary to "identify the level of technology and personnel that is really necessary" in intensive care units. The final chapter presents practical issues confronted by families whose loved ones are in intensive care units, such as the rights of the patient, evaluating the health care team, and communication between family members.

The weakest part of the book deals with discussions of specific organ systems. For example, the five major coronary risk factors are listed as heredity, lack of exercise, diet, smoking, and stress; most authorities would cite hypertension, hypercholesterolemia, and smoking as the major coronary risk factors. Similarly, current views about the effect of digitalis on congestive heart failure do not concur with the statement that digitalis can "dramatically invigorate" myocardial contractions. Also, it is misleading to suggest that the electrocardiogram is a useful tool for estimating the size of a myocardial infarction.

This book succeeds because it fills an unoccupied niche in the medical literature. Patients' families and health care workers who read this volume will have a much better understanding of the intensive care unit, including its strengths and limitations.

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Correspondence

The Editors will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words and must be typewritten, double-spaced, and submitted in duplicate (the original typescript and one copy). Authors will be given the opportunity to review the editing of their correspondence before publication.

Acoustic Neuromas

To THE EDITOR: I have just been rereading the otolaryngology Epitomes in the April 1989 issue and particularly the excellent review of acoustic neuromas.[1] These fascinating tumors were described to all of us in medical school, and we reflexively think of the diagnosis when encountering unilateral hearing loss.

Of course, the exquisite sensitivity of gadolinium-enhanced magnetic resonance imaging (MRI) scanning for acoustic neuromas has revolutionized the diagnosis in recent times.

I agree with Drs Jackler and Lanser. An effective and parsimonious strategy would be to first do a full audiogram with speech discrimination; then, if the result of the audiogram is characteristically abnormal, an acoustic brain-stem response (ABR) should be measured. The ABR is quite sensitive for acoustic neuroma and, if the result is abnormal, an MRI scan will make a final diagnosis in nearly every case.

What we were not told in medical school is that the acoustic neuroma is rare. In the largest population study reported to date, we found a yearly incidence of only 1 per 100,000 persons.[2] This is a fact that should be more widely recognized and appreciated, and it shows the necessity of using cost-effective diagnostic strategies such as those discussed above.

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Academic Medicine

To THE EDITOR: In reference to the commentary by Dr Francesco Gallatin Beuf in the October 1989 issue, I must agree with the author that academic medicine, in my opinion, is not providing the best patient care. Most full-time physicians and surgeons associated with university hospitals are more interested in their traveling professorships or their publications, which they feel they must continue in order to maintain their full-time salaries. In days gone by, when professors at teaching hospitals had large practices of their own and were respected for the expertise in their own fields, the institution did not pay these persons. They earned their own way in return for the privilege of being a professor at a university. They taught the students, and what they taught was heavily mixed with humanitarian attitudes toward patients.

I doubt very much if, on rounds these days, one sees an academic surgeon or physician sit down by a patient's bedside, hold the patient's hand, and speak in a compassionate and caring manner, or, further yet, come back after rounds to discuss directly with the patient any particular problem or question. No, rather, these leaders of medicine and surgery are more interested in getting back to their laboratories or to their transcription of the next article or the next speech that they are preparing.

I further doubt that without a thorough overhaul of the current system, we will see the likes of Professor of Medicine, Dr Francis Wood, or Professor of Surgery, Dr Isadore Ravdin, under whom I had the privilege of studying at the University of Pennsylvania in Philadelphia at a time when there were no such things as full-time academic professorships.

I write this in the hope that it will open a dialogue and a review of the way in which we are teaching our students of medicine and surgery.

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Trust

To THE EDITOR: I was somewhat surprised to see a letter in the November 1989 issue by Stuart Gherini, MD,[1] castigating me for my approach to the family and child with fulminant otitis as described in my article, "A Matter of Trust," in the August 1989 issue.[2]

The policy of many medical journals is that most letters in response to articles are sent to the author(s) for comment. Is this the policy of *The Western Journal of Medicine?* [EDITOR'S NOTE: We do it frequently but not always.]

In any case, Dr Gherini is perhaps correct in one respect—Had there been an adverse outcome I might have "had a hard time justifying [my] treatment in front of a review board of [my] peers or—worse yet—a jury." That was never an issue.

The point of the piece was not to suggest a community standard of herbal treatment of acute otitis media. That was not my approach then and is not now. It was merely to describe a fascinating case of a common pediatric illness treated in an unorthodox way with good result.

Along with Dr Gherini, I, too, recall a patient of mine 18 years ago who developed chronic suppurative otitis media leading to a brain abscess and permanent sequelae. She was a Native American girl whose parents had a large family and lived in poverty on a reservation. Although the health care system, my services, and the antibiotic medications were free to them, she likely received inadequate therapy for a variety of social and economic reasons. Would Dr Gherini consider these parents noncompliant, as he obviously did the parents in my story?

Through the luxury of the retrospectoscope, we are all geniuses, maybe even wizards. The real issue here was one of trust—thus, the title of my piece. The basic trust was in the relationship between the child's parents and me. Despite their hesitancy to accept my advice of amoxicillin and my warnings about possible dire consequences of untreated otitis, there was a level of understanding in our interaction that seemed unique to the commonplace medical encounter.

Neither the parents nor I could trust that the process would end up the way it did, with a total cure using unorthodox therapy. But in a mystical way, maybe the three of us knew something at the outset that we could not objectively define. Trust has many dimensions.

In the last of a series of articles entitled "Beyond Conventional Medicine," Flora Kelly speculates about the reasons patients seek unconventional therapy.[3] One of them is a change in the nature of the physician-patient relationship. All of us would do well to contemplate her words.

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Alcoholic Cirrhosis and Cardiomyopathy

To the Editor: The discussion by Dr Lee on the interrelationship between alcoholic cirrhosis and cardiomyopathy in the November 1989 issue was excellent.[1] As he pointed out, although alcoholic cirrhosis and cardiomyopathy share a common cause, their coexistence in the same patient is rare. In his extensive list of references Dr Lee failed to cite our paper, published in 1977, on the rare coexistence of the two conditions.[2] Of the three explanations offered by Lee—underdiagnosis, Berkson's bias, and the protective effect of low peripheral resistance in unloading the ventricles—the last seems to be most plausible.

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Is It Fair to Blame the Victim?

To the Editor: Four decades ago or so a young minister from New York City gained international prominence by preaching a catechism of hope that he called "The Power of Positive Thinking." He was Dr Norman Vincent Peale.[1]

His doctrine, which some might be tempted to reduce to a simplistic philosophy of "don't worry, be happy," struck a vital chord in the American and western European psyches and has influenced not only current pastors' messages but obviously has had a great influence on modern clinical psychology.

It is reasonable to believe that by keeping a stiff upper lip through adversity, by whistling by the graveyard in time of crisis, and by essentially adopting a doctrine of denial and keeping a positive, cheerful attitude throughout whatever the fates may bring, one may lead a happier and more productive life. That is what Dr Peale preached, and it is an all but unassailable position. Attempting to translate the quality of life to improvement in morbidity and longevity is less defensible.

So seductive is the tenet, carrying with it the unstated but subliminal implication that our state of mind can influence our health and perhaps longevity, that it has made inroads not only into theology and psychology but into clinical medicine as well. It has generated and nourished the new and arcane science of neuropsychoimmunology. Norman Cousins, formerly the editor of *The Saturday Review of Literature* and no mental lightweight, has parlayed a belief in laugh therapy into a chair at the UCLA School of Medicine, although he has gradually modified his enthusiasm for humor as medicine. There may be evidence that some stress does lower the level of helper T cells, rendering one more vulnerable to disease. Other evidence to date appears anecdotal.

So far, who can argue? The slogan, "sound mind, sound body," has reverberated through our conscious and unconscious minds for two generations. If you believe that without reservation, it is difficult to understand the existence of Stephen Hawking, PhD, who many think is the most brilliant theoretical physicist since Einstein, and whose best-selling book, *A Brief History of Time: From the Big Bang to Black Holes,*[2] was written while Hawking was so crippled by amyotrophic lateral sclerosis that he spends his entire life in a wheelchair unable to talk or write without the aid of sophisticated computer equipment. There must be another side to the coin. If one is philosophically willing to accept the benefits of the power of positive thinking, one must be willing to accept the punishment for negative thinking. It would, then, not require a Nietzsche or a Schopenhauer to conclude that if you have an accident or lose your job, it is because in some way you did not maintain sufficient positivity in your life. If you are sick and disabled, it must be in some way because you want to be.

The sick have enough misery from their illnesses. Should they now have to put up with the burden of their physicians and their relatives harboring a subliminal suspicion that it is their own fault? It would be cruel enough if it were proved. It is not. It is merely theory.

I know I am stepping on some colleagues' deeply felt belief systems. Some physicians escape their own occupational angst by a strong denial mechanism and a very strong sense of maintaining control. We all would like to feel that a positive attitude tends to confer invulnerability.

There are many ingrained folk beliefs that persist despite the lack of scientific proof. Influenced by generations of concerned parents insisting that we wear an extra sweater to school, it is still hard for some of us emotionally to accept the fact that being chilled will not make us sick. It is hard even now for me to accept the expert opinion of infectious disease specialists that being cold will not give me a cold. It always seems to.

The correlation of cancer and depression has been described in an editorial in *The Journal of the American Medical Association (JAMA)* as being centuries old.[3] I cannot

remember back quite that far, but I have always wondered whether it was the depression that caused the cancer or the far more likely probability that those patients who get cancer are likely to be depressed by their disease. And how accurately can we measure subtle degrees of depression anyway? An extensive but probably still arguable national study published in a recent issue of *JAMA*, including a survey of over 2,800 subjects, concludes that no measurement of depression currently available is a significant statistical risk for the development of cancer.[4] Particularly provocative is a quote by Angell from *The New England Journal of Medicine:*

> [T]here is overwhelming evidence that certain personal habits, such as smoking cigarettes, drinking alcohol, and eating a diet rich in cholesterol and saturated fats can have great impact on health. . . . However, it is time to acknowledge that our belief in disease as a direct reflection of mental health is largely folklore.[5(p1572)]

Before we allow ourselves the liberty of accepting that the sick somehow deserve what they get and letting that subtle judgment somehow intrude into the way we cope and care for patients, let us be absolutely sure we are right. So far, the evidence is not there.

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Book Review

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Common Skin Disorders—A Physician's Illustrated Manual With Patient Instruction Sheets—2nd Edition

Ernst Epstein, MD, Clinical Associate Professor of Dermatology, University of California, San Francisco, School of Medicine. Medical Economics Books, Oradell, NJ 07649, 1988. 110 pages, $35.95 (paperback).

Common Skin Disorders is not just another dermatologic text. It is a series of unique, concisely and clearly written chapters dealing with the most common skin conditions that general physicians see every day, including dermatitis, acne, various skin cancers, psoriasis, tinea infections, as well as dermatologic surgical procedures.

In each instance, the origin and diagnosis of the skin problem are discussed, followed by suggested therapies. Many practical and useful suggestions on therapy, which are not usually found in textbooks, are included in this book. Dr Epstein incorporates standard care with his own therapeutic suggestions.

The unique feature of this book is the very useful patient instruction sheets dealing with the topics covered in the book. The sheets are written in a style and way that should be easy for patients to understand.

Two useful appendixes are found in the book—one on how to microscopically examine for fungus and the second on sources of products, with the addresses of companies supplying dermatology materials and products.

Last, 96 photographs of the dermatologic conditions discussed in the book are presented in color, which clearly helps the reader in identifying these diseases.

A great deal of dermatologic information is presented in this text, which should be useful to family practitioners, generalists, dermatologists, and medical students.

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Case Reports

Intracranial Tuberculoma Developing During Therapy for Tuberculous Meningitis

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TEOH AND CO-WORKERS recently reported on ten patients in whom intracranial tuberculomas developed during the treatment of tuberculosis.[1] Others have reported a 4.5% to 28% incidence of intracranial tuberculomas complicating tuberculous meningitis.[2,3] We report an additional such case.

Report of a Case

The patient, a 39-year-old Filipino-American man, was admitted to hospital because of nausea, fevers, and headaches for two weeks. He had grown up in the Philippines and joined the United States military 18 years before admission. A greater than 10 mm reaction to a tuberculin purified protein derivative (PPD) skin test was noted, and his chest radiograph was normal at the time of entry into military service. He never received isoniazid prophylaxis; subsequently, he was not known to have any abnormal findings on chest radiographs. He said he had no risk factors for infection with the human immunodeficiency virus (HIV). He did not have diabetes mellitus, was taking no medications, and had no other known medical problems at the time of presentation. The results of a physical examination and a contrast-enhanced computed tomographic (CT) scan of the head were normal. An initial cerebrospinal fluid (CSF) analysis revealed the following: total protein, 1.02 grams per liter (102 mg per dl [normal, <0.40 grams per liter]); glucose, 2.6 mmol per liter (46 mg per dl [normal, 2.8 to 4.4 mmol per liter]; serum glucose, 6.2 mmol per liter [111 mg per dl; normal, 3.9 to 6.1 mmol per liter]); and a CSF leukocyte count of 532×10^6 per liter (0.97 lymphocytes and 0.03 neutrophils). An acid-fast stain was negative for microorganisms, and studies for fungi were negative. An intermediate-strength PPD test was nonreactive, and the chest radiograph was normal. The diagnosis of aseptic meningitis was made, and no antimycobacterial therapy was given.

Two weeks later the patient was admitted to Naval Hospital in San Diego because of persisting headaches and fevers. At the time of admission he was afebrile and the results of his physical examination were within normal limits. A contrast-enhanced head CT scan again showed a normal pattern (Figure 1). The specimen of CSF revealed the following: total protein, 1.40 grams per liter (140 mg per dl); glucose, 1.6 mmol per liter (28 mg per dl; serum glucose level not available); CSF leukocyte count, $1,000 \times 10^6$ per liter (0.52 neutrophils and 0.48 lymphocytes); and an acid-fast stain negative for bacilli. The chest radiograph was normal. A regimen of isoniazid, 300 mg per day, ethambutol hydrochloride, 1,800 mg (25 mg per kg per day), and rifampin, 600 mg per day, was prescribed pending the results of cultures for suspected tuberculous meningitis. After a week of therapy, the PPD test revealed 23 mm of induration. After two weeks of therapy, the patient's symptoms resolved, and he was discharged from the hospital.

Five weeks after starting therapy, he had headaches, diplopia, left hemianesthesia, and left-sided hearing loss develop over the course of a week, prompting another admission to hospital. A cranial CT scan (Figure 2) revealed mild hydrocephalus with a 2 cm in diameter, thick-walled, contrast-enhancing lesion in the right occipitoparietal area with surrounding edema. The lesion had features consistent with a

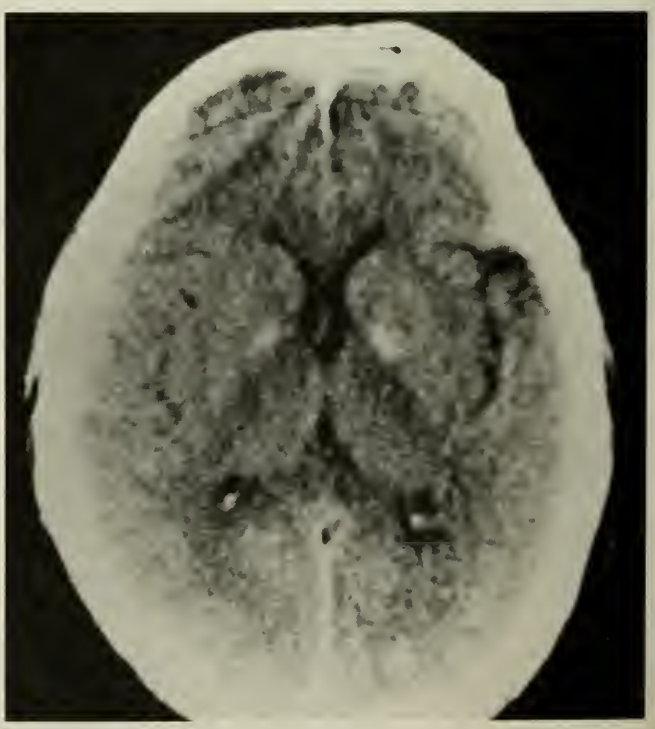

Figure 1.—A cranial computed tomographic scan taken several days after starting antimycobacterial therapy shows normal features.

(Malone JL, Paparello S, Rickman LS, et al: Intracranial tuberculoma developing during therapy for tuberculous meningitis. West J Med 1990 Feb; 152:188-190)

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ABBREVIATIONS USED IN TEXT

CSF = cerebrospinal fluid
CT = computed tomographic
HIV = human immunodeficiency virus
PPD = purified protein derivative

Figure 2.—After 6.5 weeks of antimycobacterial therapy, a 1.8- to 2.0-cm lesion (arrow) on the right side is seen, consistent with a tuberculoma.

tuberculoma, appeared to extend to the quadrigeminal plate, and was adjacent to the cerebral aqueduct, thalamus, and tentorium cerebri. The patient said that he had complied in taking his three antimycobacterial medications as an outpatient. Dexamethasone sodium phosphate was given intravenously (10 mg initially, then 5 mg every six hours), with a transient abatement of the headaches.

The CSF culture revealed *Mycobacterium tuberculosis* sensitive to rifampin and isoniazid but resistant to ethambutol and pyrazinamide. Ethambutol was discontinued, and therapy with isoniazid and rifampin was continued. Despite using intravenous steroids, however, and continued antimycobacterial therapy over the following 12 days, his headaches returned. The cranial CT scan revealed that the tuberculoma and edema were unchanged, but the third ventricle and both lateral ventricles were progressively dilated, consistent with a noncommunicating hydrocephalus. Rapid symptomatic improvement occurred after a ventriculoperitoneal shunt was

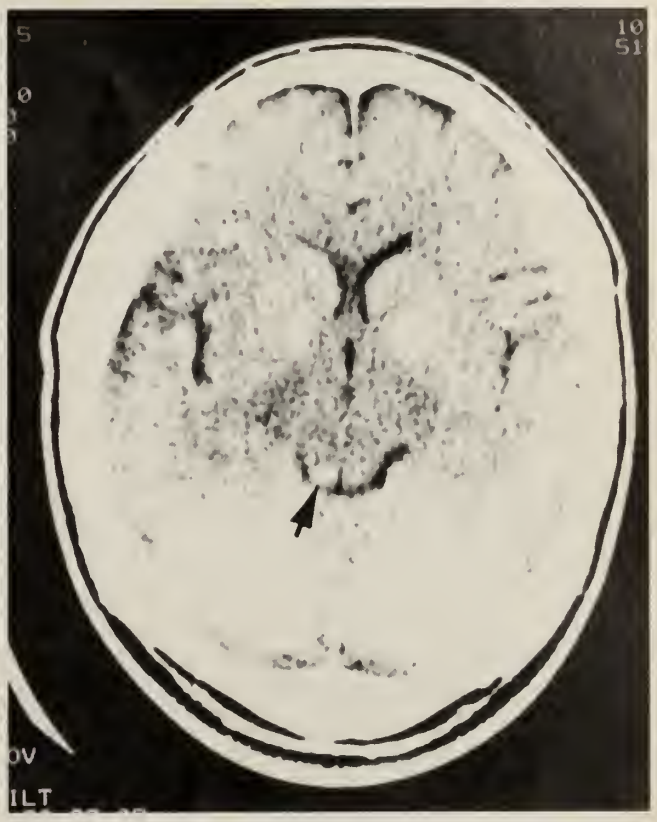

Figure 3.—A noncontrast cranial computed tomogram reveals a residual 0.8 to 1.0-cm calcified lesion in the quadrigeminal plate (arrow) approximately four years after initial presentation.

placed, and the steroid therapy was discontinued within a week. The regimen of isoniazid and rifampin was continued for 23 months. A small area of left leg anesthesia, a left partial neurosensory hearing loss, and a residual 0.8-cm calcified brain lesion seen on noncontrast cranial CT scan of the head (Figure 3) were the only abnormalities noted at 48 months of follow-up. An antibody test at a later date was negative for HIV type 1.

Discussion

The development of intracranial tuberculomas during antimycobacterial therapy is a diagnostic and therapeutic challenge for clinicians.[4-9] Our case was unusual because the culture and sensitivity results were known and, therefore, a change in antimycobacterial therapy was not required when the tuberculoma developed. Because of the eventual outcome of the case, it is evident that the transient clinical deterioration in this case was probably not due to a failure of antimycobacterial therapy.

The apparent incomplete response of the headaches and hydrocephalus to steroid therapy may have been related to the close proximity of this large tuberculoma to the cerebral aqueduct; this location may have resulted in a mechanical obstruction to cerebrospinal fluid flow at the cerebral aqueduct.[2,8] The ventriculoperitoneal shunt placement was associated with a rapid clinical improvement, and isoniazid and rifampin therapy alone resulted in a long-term clinical cure in our patient.

Although resolving completely with therapy in most patients,[10] intracranial tuberculomas are potentially fatal com-

plications.[8] Tuberculomas can result in permanent sequelae even when appropriately treated,[1] and they can be associated with residual radiologic findings at the end of therapy in as many as a third of cases.[11]

Conclusive studies concerning the use of steroids in intracranial tuberculosis have not been done,[12-14] although a regimen of steroids is often recommended when there are complications such as brain edema,[12] focal neurologic abnormalities, and hydrocephalus.[13] Definitive conclusions about the use of steroids cannot be made on the basis of our case report. Surgical intervention for intracranial tuberculoma is usually considered when medical therapy fails,[15,16] when decompression is necessary,[12,13] or when the diagnosis is uncertain.[17] The diagnosis and management of these complications can be assisted by the use of CT scans[12,17,18] and magnetic resonance imaging scans.[19]

The development of this tuberculoma during effective antimicrobial therapy and the accompanying restoration of PPD reactivity could suggest a posttreatment inflammatory reaction[14,20] or an enhanced cell-mediated immune response.[14,21] The occurrence, however, of tuberculomas in patients with negative PPD skin tests[10,22] and the reported predominance of tuberculomas in HIV-infected patients with intracranial tuberculosis[23] appear to be evidence against these proposed pathogenic mechanisms.

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Zinc Abuse—An Unsuspected Cause of Sideroblastic Anemia

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SIDEROBLASTIC ANEMIAS are disorders of the bone marrow in which a characteristic accumulation of iron occurs in the early erythrocyte precursors. This accumulation develops around the nucleus, forming a ringed structure known as the ringed sideroblast. The abnormality is often associated with severe irreversible diseases of the bone marrow such as the myelodysplastic disorders and leukemia.[1] A few disorders do not forecast such an ominous outcome as they are reversible by either treatment or withdrawal of the offending agent. Most reversible sideroblastic anemias are caused by drugs such as isoniazid and alcohol.

The patient whose case is reported here, in an attempt to "control his anger," ingested massive amounts of elemental zinc, 1 to 2 grams per day, over a several-month period, which led to the development of a sideroblastic anemia. The nature of his disorder was only determined by asking specific dietary questions relating to vitamin and mineral intake. This information was not volunteered by the patient during the routine initial history. We report his case and describe the pathophysiology of zinc toxicity and its treatment.

Report of a Case

The patient, a 34-year-old man, presented with a ten-day history of feeling tired and "run-down." He noted in addition heart palpitations and shortness of breath with minimal activity. His history was notable for the treatment of schizophrenia, which was controlled with the use of chlorpromazine, thiothixene, and benztropine mesylate. He said he did not have melena, hematuria, or a change in urine color. Three years before admission he stopped using street drugs and alcohol.

On physical examination, he was pale and obese but apparently in no acute distress. His blood pressure was 130/74 mm of mercury, and his pulse rate was 112 beats per minute and regular. He had no lymphadenopathy, petechiae, hepatosplenomegaly, or cardiopulmonary abnormalities. Some of the results of laboratory studies are shown in Table 1. Perti-

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TABLE 1.—*Laboratory Values (in Système International Units) and Response to Copper Therapy in a Patient With Zinc Toxicity*

Laboratory Component	*Normal Values*	*Day* 0	3	5	7	14	21	70
Hemoglobin, grams/liter	140-170	37.0	51.0	54.0	61.0	96.0	121	145
Hematocrit	0.40-0.50	0.10	0.15	0.16	0.18	0.29	0.37	0.43
Reticulocyte count, $\times 10^{-3}$	1-24	3	23	89	176	153	41	...
Leukocyte count, $\times 10^{9}$/liter	4.8-9.8	2.2	7.3	7.5	3.7	3.7	6.6	8.0
Serum copper, μmol/liter	11.0-22.0	0.16	...	...	5.2	...	...	11.64

nent normal values included the platelet count, the mean corpuscular volume, serum B_{12} and folic acid levels, liver function studies (except for a serum albumin level of 29 grams per liter [normal, 35 to 50]), and renal function studies. Serum iron levels, the total iron binding capacity, and saturation were normal. The ferritin level was elevated at 485 μg per liter (normal, 125 to 350). A serum zinc level determined on the second hospital day was elevated at 23.4 μmol per liter (normal, 11.5 to 18.5). A serum copper level measured at the same time was 0.16 μmol per liter (normal, 11.0 to 22.0).

Hospital Course

He received two units of erythrocytes during the first two days, with a rise in his hematocrit from 0.10 to 0.15. At this time the bone marrow aspiration done on admission was reported. Myeloid hyperplasia with vacuolation of both the erythroid and myeloid precursors was noted. Minimal megaloblastic changes were seen in the erythroid series. Iron stores were greatly increased, with 15% of the erythroblasts showing ring forms. A pronounced increase in reticuloendothelial cell iron stores was noted (4+/5). No other abnormal forms were seen in the bone marrow. The peripheral blood smear did not show any abnormalities. At this point, copper replacement therapy was begun. An intravenous solution of copper, 2 mg in 1 liter of 5% dextrose in a saline solution, was infused over 12 hours daily. This regimen was continued until discharge on day 15. No side effects were noted. By day 7 (Table 1) of therapy, his reticulocyte count reached a maximum of 176×10^{-3}. He was discharged on a regimen of copper sulfate, 2.0 mg per day by mouth. After ten weeks of oral therapy, his blood counts had become normal, and the copper therapy was discontinued. No further problems were noted. During outpatient follow-up, he confided that he had abused vitamins A, C, and D in the past.

Discussion

The use of megadoses of vitamins and minerals for a variety of reasons has become common in our society. Too much of a "good thing" can be detrimental, however. In this report, a mentally ill person, in an attempt to relieve his symptoms of rage, which he associated with an excess of body copper, ingested zinc to overcome these feelings. From anecdotal information, this patient knew that zinc interfered with the action of copper, which caused it to be depleted from the body, but he was unaware of the consequences.

Zinc and copper metabolism have a complex relationship, which is mediated through the protein metallothionein. This protein, present in several organs including intestinal mucosa, liver, kidney, pancreas, and spleen, not only is essential in zinc and copper metabolism but plays an important role in heavy metal detoxification. In part, the lowering of body copper levels by an excessive intake of zinc can be explained by the following mechanisms: Zinc induces the synthesis of metallothionein. Metallothionein binds copper in the intestinal mucosa, causing it to be sequestered and therefore unavailable for absorption.[2] This long-known reciprocal relationship between zinc and copper exists in humans as well as in animals.[3] Prasad and co-workers described hypochromia induced by zinc therapy (150 mg taken daily over 4 to 24 weeks) in patients with sickle cell anemia.[4] Using this information, Brewer and associates were able to produce a negative copper balance in several patients with Wilson's disease, a disorder associated with increased total body copper content.[5] Indeed, in premature infants, copper-deficient diets cause neutropenia, hypochromic anemia, osteoporosis, and psychomotor retardation.[6] The anemia, as currently defined, is thought to occur for the following reason: Iron is stored as ferritin in the ferric state. To be transported to bone marrow for hemoglobin formation, ferric iron must be reduced to the ferrous state, a process catalyzed by riboflavins. Ceruloplasmin is critical for the oxidation of the ferrous iron back to the ferric state. This step allows the binding to apoferritin, which is the initial step in the mobilization of stored iron. In this form, iron can be delivered to the erythrocyte progenitors in bone marrow for hemoglobin formation. Ceruloplasmin can also oxidize biogenic amines, which is thought to regulate their level.

Two cases similar to ours have been reported.[7,8] Both patients were taking self-prescribed zinc to treat "prostatitis." They both had taken the agent for at least two years at a daily dose between 200 and 400 mg. Hematologic findings were similar to those in our patient. Initial serum zinc levels were twice those we noted in this patient. Serum copper levels ranged from 0.63 to 2.4 μmol per liter. Despite stopping zinc intake, serum copper levels did not return to normal for 50 to 70 days. Our patient's leukocyte count became normal in a matter of three days. In the case reported by Patterson and colleagues, however, the leukocyte count took 63 days to become normal. It is difficult to compare the case reported here with the two previously reported because our patient stopped taking his zinc some days before admission, but the other two took zinc until admission. In another report, a person taking zinc, 660 mg a day for two years, prescribed for a malabsorption syndrome, also had similar blood findings.[9] The first two patients had classic examples of sideroblastic anemia including ringed sideroblasts in their bone marrows. No bone marrow examination was reported

for the third person, but her anemia was microcytic and hypochromic. All three persons responded to the withdrawing of zinc or to giving copper.

The physiologic requirement for zinc is 10 to 15 mg a day. Yet the suggested pharmacologic dose of zinc is ten times this amount, a dose at which toxicity has been reported. Food faddists suggest doses from 50 mg for "basic protection" to 200 mg for infertility and osteoarthritis.[10] We recommend avoiding these huge doses in order to prevent excessive intake and its accompanying toxicity. To allow for needed dietary supplementation, we recommend that over-the-counter preparations of zinc be limited to 5-mg capsules or tablets. In using zinc as a specific medication, physicians should be extremely cautious when a dose of 150 mg a day or greater is prescribed. As noted, at this "therapeutic" dose, toxicity to the bone marrow has been described. Finally, a health care team needs to carefully review a patient's history in regard to nutritional supplements. With this increased awareness, we expect more persons with self-induced vitamin or mineral intoxication will be identified.

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Herpes Zoster Phrenic Neuritis With Respiratory Failure

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HERPES ZOSTER is a rare cause of unilateral diaphragmatic paralysis, which manifestation was first described in 1949.[1] Since then, 17 cases have been reported.[2-5] We present a case of hypoventilatory respiratory failure due to unilateral zoster phrenic neuritis complicated by obesity.

(Melcher WL, Dietrich RA, Whitlock WL: Herpes zoster phrenic neuritis with respiratory failure. West J Med 1990 Feb; 152:192-194)

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Report of a Case

The patient, a 79-year-old man, had dyspnea that began in May 1987. At that time he had an aortobifemoral bypass operation complicated postoperatively by a cutaneous herpes zoster infection of the right posterior cervical region. Over the next seven months he noted progressive dyspnea, orthopnea, lower extremity edema, and daytime hypersomnolence. He said he did not have fever, cough, or chest pain. His medical history included hypertension, a right carotid endarterectomy, and a 150-pack-year tobacco history. His medications included furosemide, captopril, topical nitrates, and aspirin.

On physical examination he was obese, appeared somnolent, and was in pronounced respiratory distress with shallow respirations at 40 breaths per minute. His blood pressure was 140/90 mm of mercury. There were confluent hypopigmented scars on the right occiput, posterior neck, and shoulder (Figure 1). There was no stridor or thyromegaly. Examination of his chest revealed decreased breath sounds and thoracoabdominal asynchrony; there were no murmurs or gallops. The lower extremities showed pitting edema. There was decreased strength of the right trapezius and deltoid muscles, but otherwise muscle strength was normal. A chest roentgenogram showed a newly elevated right hemidiaphragm.

An arterial blood gas measurement done with the patient breathing room air showed a pH of 7.12, a Pco_2 of 10.8 kPa (81 mm of mercury), a Po_2 of 2.9 kPa (22 mm of mercury), and an arterioalveolar oxygen difference of 3.6 kPa (27 mm of mercury). The patient underwent emergent orotracheal intubation. There was no evidence of airflow obstruction. On fluoroscopy he had paradoxic movement of the right hemidiaphragm with a "sniff" maneuver. Computed tomography of the chest showed no mediastinal or parenchymal abnormalities. With mechanical ventilation the hypersomnolence resolved, and the patient was successfully weaned from the ventilator. He continued to manifest supine hypoventilation that was managed with nocturnal cuirass ventilation. The forced vital capacity showed a 39% decline with changing from the standing to the supine position. Table 1 shows serial changes in spirometric measurements with changes in weight. On polysomnography he had no evidence of obstructive sleep apnea, and thyroid function studies showed normal values.

During 12 months of follow-up and with a 20% weight reduction, the patient was successfully weaned from nocturnal ventilation. He has maintained normal arterial blood gas measurements despite persistent diaphragmatic palsy documented by continued right diaphragmatic elevation on repeated chest roentgenograms.

Discussion

The diagnosis of zoster phrenic neuritis was based on the findings of cutaneous lesions in the cervical dermatomes corresponding to the right phrenic nerve roots and a newly elevated hemidiaphragm that moved paradoxically under provocative fluoroscopic examination. Skeletal muscle involvement in these dermatomes was also evident. There was no evidence of causes of diaphragmatic paralysis such as

TABLE 1.—*Pulmonary Function Data and Weight in a Patient With Phrenic Neuritis*

Pulmonary Function Test	May 1987	January 1988 Standing	January 1988 Supine	February 1989
Forced vital capacity (FVC), liters*	2.76 (71)	1.93 (50)	1.38 (36)	2.31 (60)
FEV_1, liters*	2.02 (81)	1.44 (50)	1.00 (40)	1.68 (68)
FEV_1/FVC, %	73	86	...	73
Weight, kg†	96.0	92.7	...	77.7

FEV_1 = forced expiratory volume in 1 second.

*Numbers in parentheses represent the percent (%) predicted capacity.
†Ideal body weight 69.0 kg.

mediastinal tumor, trauma, cold cardioplegia, poliomyelitis, the Guillain-Barré syndrome (acute febrile polyneuritis), Parsonage-Turner's syndrome, amyotrophic lateral sclerosis, or aortic aneurysm. Phrenic nerve conduction testing was not immediately available in our case but would have supplied additional evidence for zoster phrenic neuritis.

Herpes zoster represents a myelitis involving the dorsal root ganglion, which may occasionally extend to the adjacent anterior horn cells, leading to motor involvement.[1] In 18 previously reported cases of zoster phrenic neuritis, diaphragmatic paralysis was discovered from several days to three years after the onset of zoster.[1-5] The paralysis resolved during the period of follow-up in only three cases, 1 to 18 months after zoster infection.[3-5] This clinical course parallels the known course of axial zoster neuritis for which no effective treatment has been shown.[6] A rare syndrome of brachial and phrenic neuritis of unknown cause has been reported as the Parsonage-Turner syndrome. In contrast to that of zoster phrenic neuritis, the prognosis for recovery is excellent.[7]

Figure 1.—Cutaneous lesions of healed herpes zoster are seen to involve the right second through fifth cervical dermatomes.

The causes of hypoventilatory respiratory failure can be divided into disorders of ventilatory drive, ventilation-perfusion, neuromuscular function, and thoracic compliance. The respiratory consequences of unilateral diaphragmatic paralysis include a substantial decrease in functional residual capacity and vital capacity; however, hypoventilation is not reported to be a feature of uncomplicated unilateral diaphragmatic palsy.[8] Similarly, the respiratory complications of obesity include a decreased functional residual capacity and decreased thoracic compliance resulting from excessive body mass.[9] As with diaphragmatic paralysis, these effects are most prominent in the supine position.

This patient experienced an excessive work of breathing because of his obesity. We postulate that the added mechanical liability of a paralyzed hemidiaphragm resulted in progressive alveolar hypoventilation. Successful management was accomplished with weight reduction to decrease the work of breathing and with interim management of positional hypoventilation with nocturnal cuirass ventilation. Negative-pressure ventilators and other forms of noninvasive mechanical ventilation have been used effectively to provide intermittent ventilatory support for patients with compromised respiratory muscle function as seen in cases of poliomyelitis and muscular dystrophy.[10]

This is the first report of unilateral zoster phrenic neuritis associated with respiratory failure complicated by obesity. The cutaneous stigmata of herpes zoster with a newly elevated hemidiaphragm was diagnostic of zoster phrenic neuritis.[3] Hypoventilation, manifested by a preserved arterio-alveolar oxygen difference, suggested a neuromuscular disorder as the cause of respiratory failure. The respiratory consequences of excessive work of breathing due to obesity and compromised neuromuscular function caused by zoster phrenic neuritis were cumulative. Therapy with short-term negative-pressure nocturnal ventilation combined with weight loss was effective.

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Book Review

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

Preventing Emergency Medicine Malpractice

Raymond M. Fish, PhD, MD, Burnham City Hospital Trauma Center and University of Illinois, Urbana-Champaign, and Melvin E. Ehrhardt, MD, JD, Mennonite Hospital, Bloomington, Illinois. Medical Economics Books, Oradell, NJ 07649, 1989. 167 pages, $31.95.

Preventing Emergency Medicine Malpractice is a small volume full of case histories of emergency medicine malpractice and good common sense advice on how physicians practicing in emergency departments can avoid these situations. This book does a good job of classifying the potential problem areas that lead to emergency medicine malpractice and gives a reasonable overview of high-risk situations such as AMA (against medical advice) patients, psychiatric problems, abuse and assault cases, and the most common misdiagnoses that lead to malpractice claim judgments. The weakness of this book lies in its lack of strong, in-depth reviews of many of these identified problem areas. The discussions include many case reports, sometimes with legal references, but a clearly referenced explanation of the laws applicable to particular situations is often lacking. For example, in its section on "Patient Transfers and Dumping," the only reference to COBRA legislation is the sentence "COBRA legislation imposes severe penalties for some financially motivated transfers."

This book, however, is not meant to be an in-depth review of malpractice legal doctrine, and in terms of its purpose of highlighting problem areas and giving practical advice, such as the recurring emphasis on complete and specific documentation of the medical record, it has much to offer. The chapter on "Emergency Consent and Refusal of Treatment" is an excellent review, particularly of how to deal with the patient who wants to leave against medical advice. Some specific suggestions are offered on what to document in the record regarding this situation. I also found the chapter on "Medical Records" to be a good discussion of one of the most essential areas of risk management—documenting the medical record. The chapter on "Handling Psychological Problems in the Emergency Department" was a helpful discussion of a stressful and problem-prone area of emergency medicine but was somewhat weak on giving specific details and advice on psychiatric commitment, two-physician holds, police holds, and the particular rights and duties of physicians in these situations. Again, because of variances from state to state, an in-depth discussion is probably beyond the scope of a book this size.

The chapters on "Lawsuit Danger Signs" and "Common Lawsuits in Emergency Medicine" again are reasonable overviews of some common risk management pitfalls and the medical conditions that lead most frequently to emergency medicine lawsuits, such as myocardial infarctions, fractures, meningitis, wounds, and appendicitis. The discussion of these specific syndromes is filled with anecdotal case reports and common sense advice for how to avoid trouble with these diagnoses, but for the physician looking for good data, useful information from clinical trials, and strong, clinically oriented, in-depth discussions of these particular areas of medicine, this volume does not go into enough detail or give adequate references on these issues.

ROBERT EICHNER, MD
Director of Quality Assurance
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Lessons From the Practice

Fleeting Moments

KIRSTI A. DYER, MS, *Davis, California*

I was an emergency medical technician: young, inexperienced, and anxiously awaiting the next call.

3:00 PM "Female, down embankment, Pinecrest Lake. Send ambulance." The call is in. I wait an eternity for my partner to arrive. Marty is on a pager at home, responding only when needed. I listen to the seconds tick.

3:10 PM Marty dashes into the station. We leave in an instant and head toward Pinecrest Lake.

3:17 PM We finally arrive at the lake. It takes a few more minutes to load ourselves and the gear into a waiting boat. The victim is down by the spillway, halfway around the lake, at least 30 to 40 minutes away by foot; with equipment it is ludicrous for us to even try to reach her on foot.

Skimming across the water, I now have the chance to think. This point in a call is invariably the worst for me, wondering what awaits us at the accident site. The questions race through my head. Can we get to her? Did we bring enough gear? Did I remember to bring splints? Should I have brought a litter? Will Marty and I, both women, be able to do anything other than just try to stabilize her, then wait for back-up? Maybe we can recruit the boat driver. Will the victim be accessible, or will we have to call the search and rescue squad for their extrication expertise? Should we have initially alerted search and rescue? What kind of condition will the victim be in? The report, as usual, is sketchy. My greatest concern is, how long has she been down?

3:32 PM We reach the far side of the lake. Since the distress call, 32 minutes have elapsed, but it seems like forever. Mentally calculating, I add a minimum of 30 minutes, the time required for her companion to hike out to the marina and place the call. God, we are talking about at least an hour since her friend left the accident site. Who knows how long it took for her to realize she had to get help? Was it instantaneous, or did she wait a millennium? For a mountain community, a response time of an hour is fairly fast.

We are now at the embankment, within minutes of the accident site. All that is left is to grab the gear and go. The report states she is down by the spillway. Crazy kids, don't they even bother to read the posted sign: KEEP OFF ROCKS? I guess all kids believe they are immortal. We are probably looking at a broken arm or leg, which will require splinting, bringing her back to the boat, and then transporting her via ground ambulance. If the injury is really bad, a head injury, for example, then Medi-flight will be needed. With jump kit in hand, I follow Marty down the steep trail adjacent to the spillway, trying to concentrate on my footing and ignoring the familiar sick feeling in my stomach. I always feel sick to my stomach by the time I reach an accident site. I often wish I could learn to thrive on the adrenaline the way others in emergency work seem to, but instead I just feel nauseous from too much apprehension, dread, and anxiety over what is waiting—fear of the unknown.

3:42 PM We locate the accident site at long last and discover the victim. My God, what happened? I have to remain calm. I must keep my composure. I cannot panic. I must be a professional. But she is dead. The report said nothing about her being dead. She is just lying there with an enormous boulder on her chest. Can it be moved? No, it is too large; we are going to need additional equipment. Check for pulses. No pulse. Begin CPR. I cannot. She has a boulder on her. It is impossible to reach her chest. Besides, she is cold, blue, and as far as I can calculate, has been down for at least an hour. We should have gotten here sooner. We should have driven faster in the car, in the boat. We should have moved more quickly. If only we had. . . .

3:00 PM Nine years later.

I responded to that call in the summer of 1980, but the frustration of not being able to do more still haunts me. With the hindsight of a first-year medical student, I see that there was nothing more that we could have done, even if we had been on the scene at the very instant the boulder fell, the very second that life left her body. She was cyanotic, cold, and stiff with rigor. The boulder crushed her chest, so she had certainly died instantaneously from either a ruptured heart or aorta, some type of massive internal bleeding. It also would have been impossible for her to keep her brain perfused; she could not breathe.

I remember watching her lying there and thinking about how her family would take the news. She had been on vacation with friends, not with her parents. I wondered how her companion would cope, especially if she had been the one climbing up first, the one who had loosened the boulder. I did not know then how much this call would affect me for years to come. She was just 15, only three years younger than I. I would not realize until many years later that we both lost our youth on that day.

(Dyer KA: Fleeting moments. West J Med 1990 Feb; 152:195)

Ms Dyer is a second-year medical student at the University of California, Davis, School of Medicine.
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Lessons From the Practice

Bernstein's Hug

ELLIOTT B. OPPENHEIM, MD, *Bellevue, Washington*

Uncle Phil joined the glowing soldering iron to the wire where it entered the hen house. Blue acid smoke, the vapors of lead and tin, curled off the twisted wires. Then he stroked the splice three or four times with a wire brush to remove the silvery solder residue. Just as he said, "There, that'll do ya," with great satisfaction at our work, a squadron of wasps flew an attack mission right at my face. The hole where the wire entered the hen house was the secret entry to their air base.

Although I was only 4, I remember jumping from the ladder—what seemed a perilous distance—and as I sank to the ground, my face and shoulders were engulfed by a million stings. Uncle Phil scooped me into his large farmer arms, and I recall the smell of wood dust and solder all over him and the sour smell of fear creeping from his woolen shirt as he cradled me against his chest.

Aunt Phyllis coated the stings with some mud she kept in a jar, but I felt sick and vomited. "He don't look too good, Philly," she said, as everyone gathered in the kitchen to assess the situation. "He looks like a tomato." Uncle Phil spoke in the measured, somewhat puzzled and thoughtful tone he reserved for serious considerations, completely missing the obvious humor. "Where's Dora and Leon?" There was a waver of terror in his firm baritone.

By this time I was a balloon and could barely see. My eyelids dropped into my visual fields as my little fingers swelled to cocktail-sausage proportions.

"I . . . I . . . can't breathe, Uncle Philly." I could not get a breath or even squeeze one out.

Aunt Phyllis panicked. "Philly, he's gonna die! Where's Dora and Leon?"

When I heard the word "die," my heart bounded from a cha-cha straight to a flamenco.

Somewhere far off in the distance, I heard my dad and mom coming. "Ellie, Ellie!" I heard my mother shrieking. Then there was a cool, quiet period like drifting effortlessly without sound.

"Okay, little guy, okay," said the doctor as a green face filled my eyes. My body was on fire. Down between my legs, my southern parts were aflame and itched. "Look out!" cautioned the doctor as I shot a stream across his examining room. "His six-shooter's working fine. . . . He's going to be all right!"

The doctor stabbed me again in the thigh, "This'll hurt, little fella." After the injection, my heart rapped out a fast military march, a train roared in my ears, and I threw up again . . . but I could breathe . . . and see. The picture was no longer green. "Almost lost you, big guy. Almost lost you."

The physician was a bearded man—a white beard as I recollect—whose hands smelled of antiseptic and who held what seemed like, to my 4-year-old eyes, a whaling harpoon. "No more of these," he reassured me and patted my head.

The fire storm abated, and I felt so much better. I sat in the doctor's lap with my nose up against his chest, dazed, yet feeling his muscular arms around me as I sniffed his aftershave, same as my dad's.

"He don't look like a tomato no more, Doc . . . good job," Uncle Phil quipped, but this time the humor had its effect as a deep satisfying ripple calmed the group.

The physician—his name was Bernstein—held me until my heart returned to a waltz tempo. I was so tired after the ordeal. "Here, Mr Oppenheim, here he is . . . better tell him to stay out of those wasps," Dr Bernstein said as the entourage emptied from the country office.

As I look back at it now, even at that tender age I identified with Doctor Bernstein and remember the fragility I felt with him, yet the comfort in the love with which he treated me; his strength, his muscles of sinew, and those muscles of knowledge that surrounded me. So sure and careful he was in his treatment.

Physicians occupy such a precious position in our web of life. Today, almost 40 years later, I care for and love my patients in the way I was taught. Sometimes, when I think it is beneficial, I give my patients a Bernstein hug to let them feel the ancient powers of healing. I bring them the courage and the confidence, the love and the knowledge that originated when humans began caring for humans. This was an example I learned when Doctor Bernstein saved me from anaphylactic shock in Colchester, Connecticut, in August 1951.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Series' Editors

(Oppenheim EB: Bernstein's hug. West J Med 1990 Feb; 152:196)

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Premiums are set by doctors on the SCPIE Board of Governors who pay those premiums themselves. They strive to hold costs as low as possible, while keeping SCPIE strong and solvent. If premiums turn out to be more than needed to pay claims and costs, the excess is returned.

SCPIE is on top of the leader board. It's worth a call to find out what we can do for your retirement game.

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scpie

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Los Angeles, CA 90067
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(619) 544-0163
(In San Diego County)

(Continued from Page 198)

PHYSICIANS WANTED

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A dynamic and growing 65-physician Southern California medical group network, has immediate career opportunities for primary care physicians. Examine our benefits:

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- Paid malpractice;
- Medical & dental plans;
- Retirement, disability;
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SAN FRANCISCO NORTH BAY AREA/NAPA VALLEY. Immediate openings (career and part-time) in a multidiscipline Emergency Department for physicians trained in Emergency Medicine, Internal Medicine, Family Practice, or Pediatrics. Full in-house multispecialty coverage. Complete generous benefit package. Contact Robert Mack, MD, Kaiser Hospital, 975 Sereno Dr, Vallejo, CA 94589; (707) 648-6200. EOE.

CALIFORNIA, NORTHERN. A stable group of four ABEM certified/eligible MDs at coastal hospital of 24,000 patient visits would like two new associates. Income $60-$75 per hour. Will consider Family Practice but prefer Emergency Department trained Emergency Physician. Coastal paradise near redwood national parks, minutes from Klammath, Rogue, and Smith Rivers. Video tape of area available. Send CV to EPMG, 120 Montgomery St, Ste 1000, San Francisco, CA 94104.

GIG HARBOR, WASHINGTON—INTERNIST. Excellent opportunities in rapidly growing bedroom community for Tacoma and Seattle. Existing medical complex has 19 different health care professionals. Build to suit or finished space available. Information—Dr Jon H. Kvinsland, 5122 Olympic Dr NW, #A201, Gig Harbor, WA 98335; (206) 851-9171.

ARIZONA. Established Emergency Medicine group has immediate openings for full- or part-time BC/BE physicians seeking career opportunity in busy Emergency Department with excellent location and case mix. Flexible schedules, excellent living and working conditions. Compensation range $150K to $200K for full-time. Send CV in confidence to General Manager, PO Box 80412, Phoenix, AZ 85060-0412.

PHYSICIANS WANTED

GASTROENTEROLOGIST — SAN DIEGO. Thriving multispecialty private practice group seeks Gastroenterologist. The practice offers excellent opportunity to enjoy growing group, see private and managed care patients and build stable future. Compensation includes guarantee plus incentives and benefits. Please send CV to Miriam Stephens Drake, 1450 Frazee Rd, Ste 305-1, San Diego, CA 92108; or call (619) 295-0599.

URGENT CARE/PRIMARY CARE PHYSICIANS for over 90 positions available with various physician groups in Phoenix metropolitan/Tucson, Arizona. Excellent compensation and partnership opportunities. Contact Mitch Young, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

RADIOLOGIST. Immediate opening for BC General and Diagnostic Radiologist at teaching hospital near Seattle. Ultrasound, CT, and mammography, plus limited basic angiography and interventional skills. Washington license not required. Regular hours. Full-time or six to nine months per year. Five-year contract. Call Dr Bernstein, (206) 840-9652.

SOUTHERN OREGON. BC/BE Family Practitioner to join busy five doctor Family Practice group summer 1990. Practice is located in the Rogue Valley, which is amply endowed with cultural events and outdoor activities. Affordable housing in area of low seismic potential. Admission privileges available at two local hospitals. OB optional. Guaranteed salary and benefits with option to join group after one year. Send CV to Daniel Heyerman, MD, Central Point Medical Group, PC, 524 Manzanita, Central Point, OR 97502.

SALT LAKE CITY, UTAH, FAMILY PRACTICE PHYSICIAN, BC/BE. Excellent opportunity in Salt Lake suburb to join busy practice, near excellent skiing, hunting, and fishing. Our clinic operates six days a week, and our patients are from a growing Salt Lake suburban population. Excellent salary and benefits. A partnership opportunity will be available after two years. Send CV to Robert Davis, MD, Director, Family Medical Center, 1781 W. 90th S., West Jordan, UT 84092; (801) 562-9100.

UTILIZATION REVIEW POSITIONS

Cost Care, the nation's leading independent utilization management company, is seeking BC physicians to staff the medical services department. These part-time positions will include intensive training in all aspects of health care cost containment including pre-certification, home health care and case management. Prior Utilization Review experience is a plus, but not mandatory.

If you are seeking new skills in the changing health care marketplace, please submit your CV to:

Alan R. Greenfield, MD, MBA
Vice President
Medical Services
COST CARE, Inc
17011 Beach Blvd, Ste 400
Huntington Beach, CA 92647

PHYSICIANS WANTED

OBSTETRICS/GYNECOLOGY CONSIDER CALIFORNIA'S NORTH COAST

Exceptional opportunity to have a quality, thriving solo or partnership practice with coverage. There is a real need for an additional OB/GYN to establish a practice to keep pace with the expansion of our well equipped/full-service hospital, including the doubling of our OB department and referral base. University community on the beautiful redwood coast has superb educational, cultural, and recreational activities. Adjacent office space is available. BE/BC physicians should call and/or send CV to:

Physician Recruitment Committee
Mad River Community Hospital
PO Box 1115
Arcata, CA 95521
(707) 822-3621, ext 249

CALIFORNIA, NORTHERN. Full-time Emergency Medicine staff positions available in 230-bed teaching hospital in Stockton with 50,000 annual visits. Teaching programs in Internal Medicine, General Surgery, Family Practice and Obstetrics/Gynecology. Excellent, prompt specialty back-up. Malpractice, health, and dental provided. Flexible scheduling, $100,000 plus annually. Contact Richard N. Buys, MD, PO Box 1020, Stockton, CA 95201; (209) 468-6818. AA/Equal Opportunity Employer.

WANTED: BC/BE FAMILY PRACTICE OR INTERNAL MEDICINE/PEDIATRICS with Emergency Medicine experience for second physician in our Emergency Department. ACLS/ATLS required. Boise offers a variety of cultural activities and is close to skiing, hunting, fishing, white water. Contact Idaho Emergency Physicians with CV at 2312 N. Cole Rd, Ste B, Boise, ID 83704.

CARDIOLOGIST. BC/BE sought to join a large hospital based multispecialty clinic. University affiliated residency program. Excellent fringe benefits. Competitive salary. California license required. Send CV to Aung-Win Chiong, MD, The Permanente Medical Group, Inc, 2025 Morse Ave, Sacramento, CA 95825. EOE.

BC/BE FAMILY MEDICINE/INTERNAL MEDICINE needed for well established, comprehensive clinic in sunny San Diego. English and Spanish a plus. Contact Rhonda Simpson, MD, or Marielena Covarrubias, (619) 234-8171, or send CV to Logan Heights Family Health Center, 1809 National Ave, San Diego, CA 92113. FAX (619) 237-1856.

CENTRAL CALIFORNIA. Join our team of Family Practice Physicians in a progressive community health center near Fresno, California. Competitive salary with extra on-call and overtime. Malpractice paid. Generous vacations and time-off policy. Affiliated with UCSF with on-site Family Practice residents and medical students. Varied practice, including Obstetrics, Pediatrics, and in-patient care with an emphasis on health maintenance, patient education, and primary care research. Position is 60 percent clinical, 40 percent teaching. Bilingual English-Spanish helpful. Contact Ardeth Bier, Fresno County Dept of Health, PO Box 11867, Fresno, CA 93775;. (209) 445-3353.

SACRAMENTO AMBULATORY / URGENT CARE. Family Practitioners/Internists needed to staff adult urgent care center in Sacramento. Part-time shifts available. Clinic operates seven days per week, 12 hours per day. Excellent hourly remuneration. Benefits possible. Contact Stuart Hahn, MD, (916) 973-5546, or request application from Carolyn Whelan, Physician Recruiting, The Permanente Medical Group, Inc, 2025 Morse Ave, Sacramento, CA 95825. EOE.

(Continued on Page 201)

A graduate of the University of Oklahoma, Jeffrey Davis, M.D., joined FHP in 1982 after completing his Family Practice residency at St. Mary-Corwin Hospital in Pueblo, Colorado, and 5 years of private practice in Oklahoma. A member of the American Board of Family Practice, he is now Chief of Staff of FHP Hospital in Fountain Valley, California.

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Providing high quality patient care is your number one priority. As one of the nation's largest physician-run HMOs, FHP shares your priorities. In order to provide the highest quality care to our members, we give our physicians the freedom to concentrate on what really matters—their patients.

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Join an organization that gives you what you need to practice high quality medicine. Call us toll free at 800-336-2255 (in California) or 800-446-2255 (outside California). Or send your CV to: FHP, Professional Staffing, Dept. 99, 9900 Talbert Avenue, Fountain Valley, California 92708. Equal Opportunity Employer.

Giving Physicians More Of What They Want

FHP® HEALTH CARE

(Continued from Page 200)

CALIFORNIA—NORTH SAN FRANCISCO BAY AREA. Excellent opportunity for BC/BE Family Practitioner to join our growing department in Fairfield. Multispecialty clinic emphasizing personalized care. Full hospital privileges including ICU/CCU, but no Obstetrics. Very favorable call schedule. Prepaid HMO practice provides excellent salary, benefits. Forward CV to Steven Freedman, MD, Kaiser Permanente, 1650 Gateway Blvd, Fairfield, CA 94533; (707) 427-4260. EOE.

FAMILY PRACTITIONER. Steinbeck country, BC/BE Family Practitioner to join dynamic group; includes hospital care, shared call. Spanish helpful. Many visiting consultants, good guarantee with chance for early partnership. Many fringes. One hour to Monterey, three hours to San Francisco. Call or write Helen Poole, 210 Canal St, King City, CA 93930; (408) 385-5471.

EUGENE CLINIC, EUGENE, OREGON

Dynamic 55 physician multispecialty group with seven locations seeks BC/BE physicians in the following specialties: Family Practice, Geriatrics, Occupational Medicine, Orthopedics, Psychiatry, Urgency Care, Urology. Eugene, attractive university town within 60 mile radius of Cascade Mountains and Oregon coast, offers superlative life-style, fine school system, active and varied cultural opportunities, and unlimited recreation. Qualified candidates send CV and three letters of reference to:

Physician Recruiter
1162 Willamette St
Eugene, OR 97401

CALIFORNIA AND WESTERN STATES

Opportunities for BE/BC physicians in metropolitan and rural areas in ENT, Family, General Surgery, Internal Medicine, Nephrology, Neurology, Neurosurgery, Plastic Surgery, OB/GYN, Orthopedics, Pediatrics, Pulmonology, Rheumatology, Urgent Care, and Urology.

Bradshaw Associates, 21 Altamount, Orinda, CA 94563
(415) 376-0762, FAX (415) 376-0813.

SACRAMENTO KAISER PERMANENTE. BC/BE Family Practitioners needed to join large group of Family Practitioners providing ambulatory and inpatient care in a large prepaid health plan. Excellent working environment with strong specialty support. Outstanding financial package. Sacramento is a growing metropolitan area with good schools and recreational activities. Close to San Francisco and Lake Tahoe. If interested, please contact Stuart Hahn, MD, The Permanente Medical Group, Inc, 3240 Arden Way, Sacramento, CA 95825; or call (916) 973-5546. EOE.

EMERGENCY PHYSICIAN to join established group at attractive, well-equipped emergency room, with excellent nursing, attending staff, in San Francisco. $100K per year. Malpractice paid. Contact Rob Hemmick, MD, 450 Stanyan St, San Francisco, CA 94117; (415) 750-5700.

PHYSICIAN WANTED. Full-time General Internist/Family Practitioner BC/BE, to join primary care group in San Diego area. Excellent salary, bonus, and benefits. Send CV to Douglas P. Mooney, Medical Director, 1011 Camino Del Rio S., Ste 450, San Diego, CA 92108.

ORTHOPEDIC SURGEON AND NEUROSURGEON. BC for well established disability evaluation office in Sacramento. Full- or part-time, regular weekday hours, benefits available. Send CV to PO Box 160408, Sacramento, CA 95816.

SAN FRANCISCO PENINSULA (SAN MATEO). Two Internists seeking associate for General Internal Medicine practice in San Mateo on San Francisco peninsula. A 250-bed hospital one block from office. Weekly continuing medical education program in the hospital by Stanford professors. Ideal weather. Mountains and ocean nearby. Excellent call rotation. 18 miles from Stanford and University of California medical schools. Guaranteed income. Send résumé to Stephen Marks, MD, 109 St. Matthews Ave, San Mateo, CA 94401; (415) 343-2737.

SAN FRANCISCO BAY AREA. BE/BC Internist. We currently are seeking highly qualified Internists and subspecialists to complement our energetic Internal Medicine team. Department members provide a full range of medical services for a population of over 200,000 prepaid Health Plan members. Recently renovated and expanded medical center facilities are within convenient commuting distance to virtually any bay area city and the extensive cultural and recreational activities of northern California. As part of our large, multispecialty group practice, you would enjoy an excellent salary, generous fringe benefits, a flexible schedule, and the opportunity for academic affiliation with prestigious local institutions. Send CV to Winslow Wong, MD, Attn: Administration, Kaiser Permanente Medical Center, 27400 Hesperian Blvd, Hayward, CA 94545. EOE.

GENERAL INTERNIST, BC/BE, needed for a position with suburban satellite clinic of a Seattle area, multispecialty group practice. Diverse patient population includes managed care, fee-for-service, retired and active military. Competitive salary and excellent benefits. Contact Mary Anderson, Pacific Medical Center, 1200 12th Ave S., Seattle, WA 98144; (206) 326-4111.

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(Continued from Page 201)

PHYSICIANS WANTED

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Good People Good Medicine

NORTHERN CALIFORNIA

Several positions available for Family Practice, Internal Medicine, and most medical subspecialties. We are a young, aggressive group in a well known prepaid group practice HMO organization with excellent benefits and a very reasonable call schedule. You will have a rewarding practice opportunity with ample time to enjoy the mountains and San Francisco which are nearby. If interested please call or send CV to Physician Recruitment, Administration, The Permanente Medical Group, Inc, 1305 Tommydon St, Stockton, CA 95210; (209) 476-3300.

NORTHERN CALIFORNIA—SAN FRANCISCO BAY AREA. Leading HMO is seeking BC/BE physician to staff a busy urban, full-service Emergency Department with the possibility of administrative advancement. Kaiser Permanente is a large pre-paid HMO offering competitive salary, job security, shareholder status, and generous benefits including health care, life insurance, disability insurance, sick leave, mortgage assistance, and educational leave. Please address all inquiries to David Witt, MD, Emergency Dept, Kaiser Permanente Medical Center, 1200 El Camino Real, South San Francisco, CA 94080-3299; or call (415) 742-2516. EOE.

GENERAL INTERNIST. Steinbeck country, BC/BE General Internist to join dynamic group; includes hospital care, shared call. Spanish helpful. Many visiting consultants, good guarantee with chance for early partnership. Many fringes. One hour to Monterey, three hours to San Francisco. Call or write Helen Poole, 210 Canal St, King City, CA 93930; (408) 385-5471.

SAN FRANCISCO BAY AREA. Internal Medicine/Family Practice/Emergency Room trained physician sought for growing primary care private practice in new facility near hospital in attractive, growing suburban community. Current practice has one full-time, one part-time physician, and one full-time physician assistant; plans exist for primary care group up to four physicians. Competitive salary first year with benefits and bonus; then eligible for partnership. Send CV to Sandra Colville, ValleyCare Health System, 4637 Chabot Dr, Ste 304, Pleasanton, CA 94588; (415) 373-4109.

PEDIATRICS, SAN FRANCISCO BAY AREA. Growing, affordable suburban area. Two private Pediatric group practices seek full-time/part-time associates. One general practice on hospital campus; one two-location practice which emphasizes inpatient and neonatal care. Competitive salary and benefits offered, and partnership opportunity. Affiliation with community hospital building state-of-the-art MCH facilities and level II nursery. Send CV to Sandra Colville, ValleyCare Health System, 4637 Chabot Dr, Ste 304, Pleasanton, CA 94588; (415) 373-4079.

PHYSICIAN OPPORTUNITIES NATIONWIDE

For all specialties for hospitals, clinics, multispecialty groups, partnership and solos. Contact Jim Grant in complete confidence at the bay area specialists, **Nugent & Grant, Inc, 1400 Coleman, Ste B-22, Santa Clara, CA 95050; or call (800) 727-2478, FAX # (408) 727-7390.** Never a fee to the physician.

PHYSICIANS WANTED

SPINE SURGEON, SOUTHERN CALIFORNIA

An Orthopedic Surgeon with training in Spine Surgery is needed to join two busy, well established Orthopedic Surgeons in Los Angeles County. Unlimited potential since this expertise is not represented in the group's service area. For more information about this opportunity, call toll free 1 (800) 626-1590, or send your CV to

Gordon Crawford, Professional Relations
Humana Inc, Dept HH-2
500 W. Main St
Louisville, KY 40201-1438

ALL SPECIALISTS NEEDED. Excellent opportunity for physicians wishing to increase Worker's Compensation and Personal Injury defense evaluations and treatment in either your office or ours. Part-time and full-time positions available throughout California with a large, well established medical management company. Please contact Linda, (714) 565-3267 for information.

WANTED: GENERAL INTERNIST to join six progressive Family Physicians in northern California vacation wonderland. Opportunity to practice practical medicine, both primary care and referral. Salary/benefits negotiable. Siskiyou Medical Group, PO Box 339, Mount Shasta, CA 96067; (916) 926-6309.

WANTED: OBSTETRICIAN/GYNECOLOGIST to join six progressive Family Physicians in northern California vacation wonderland. Both primary care and referral practice. Salary/benefits negotiable. Siskiyou Medical Group, PO Box 339, Mount Shasta, CA 96067; (916) 926-6309.

NORTHRIDGE OUTSTANDING OPPORTUNITY for Internist with/without subspecialty in San Fernando Valley area of Los Angeles. Very large mixed subspecialty consultative practice in Hematology/Oncology and Internal Medicine. Fee-for-service, PPO, and HMO patient base in small group private practice. Teaching encouraged. Association with possibility of partnership. Available March 1990. Call Lorna, (818) 886-8550.

PRIMARY CARE, GENERAL INTERNIST OR FAMILY PRACTITIONER BC/BE to join established Internist in satellite clinic 10 miles from main clinic across state line in Oregon. Main clinic is an expanding 31 physician multispecialty group. Guaranteed income plus excellent benefits. Send CV to Connie Goude, 55 W Tietan, Walla Walla, WA 99362.

PHYSICIAN ADMINISTRATOR
Southern California

CIGNA Healthplans of California—a staff model HMO committed to providing innovative, quality health care to 400,000 members in southern California—is seeking a Primary Care Physician to assume the challenging responsibilities of Physician Administrator at one of our 30 health care centers.

You will maintain an active clinical practice with a proportion of time dedicated to leadership and management of physician and support staff. Qualifications must include Board Certification in a clinical specialty and prior management experience. Excellent compensation and benefit package, including bonus plan.

Call collect or send CV in confidence to:

Robert Harrington, MD
Professional Recruitment Dept
CIGNA Healthplans of California
505 N. Brand Blvd, Ste 400-49
Glendale, CA 91203
(818) 500-6570

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Physicians and Surgeons

OREGON/SOUTHWEST WASHINGTON

Excellent opportunities available for BC/BE Family Physicians in Oregon and southwest Washington. Openings available in the Portland/Vancouver area (full-time and half-time); Longview, Washington; and Salem, Oregon. Group provides a full range of professional services to 20,000 to 380,000 Kaiser Permanente members depending on location. Excellent salary/benefits; senior physician standing after two years; sabbatical; paid liability coverage.

Forward CV and inquiry to

Regional Medical Director
Northwest Permanente
3600 N. Interstate Ave
Portland, OR 97227.

CALIFORNIA CENTRAL COAST. Seeking BC/BE Family Physician to join established group of 11 BC physicians in a smog free, family oriented, growing community north of Santa Barbara. Full range of Family Practice including Obstetrics. Guaranteed competitive salary plus excellent benefits. Opportunity to become full partner after one year. Send CV or call William Diebner, Administrator, 136 N. Third St, Lompoc, CA 93436; (805) 736-1253.

FAMILY PRACTICE PHYSICIAN. Full-time in a busy walk-in medical clinic. Located in Visalia, California (Tulare County). Malpractice insurance, good salary, etc. Please call (209) 627-5555 for more information.

PEDIATRICIAN. University affiliated multispecialty group seeks a BC/BE Pediatrician to function in a primary care capacity in Fresno, California. Outstanding opportunity for personal growth and involvement in a growing group practice. Position available immediately. Competitive salary and paid malpractice. Send CV to John Riggs, MD, Medical Director, 2212 N. Winery, #130, Fresno, CA 93703. Equal Opportunity Employer.

SAN DIEGO. Well established multispecialty group composed of Family Physicians, General Internists, OB/GYNs, Pediatricians, General Surgeons, ENT, and Ophthalmologist is expanding. Those interested in joining a vital private practice group, with emphasis in primary care and seeing fee-for-service and managed care patients, are welcome to send CV to Miriam Stephens Drake, 1450 Frazee Rd, Ste 605-1, San Diego, CA 92108; (619) 295-0599.

PATHOLOGY DIRECTOR, SOUTHERN CALIFORNIA—BC clinically/anatomically trained with three to five years community hospital director experience needed to run pathology dept in 230-bed community hospital. Beautiful beach location in moderate sized city with excellent outdoor activity opportunities. Send CV to Administration, Community Memorial Hospital, Loma Vista at Brent, Ventura, CA 93003; or call (805) 652-5005.

PUGET SOUND. BC/BE Family Practitioner needed to join three other well established young Family Practitioners in successful half-time practice 30 minutes from Seattle. Strong Family Practice community. Excellent consultant relationships. Obstetrics optional, but preferred. Beautiful area with ample recreational and cultural opportunities. Contact Dan Goodman, MD, 1111 Pacific Ave, Everett, WA 98201; (206) 259-7255.

(Continued on Page 203)

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PHYSICIANS WANTED

PROGRESSIVE MULTISPECIALTY GROUP

of over 20 physicians, located in Tracy, one of the most rapidly growing cities in northern California. Located in the San Joaquin Valley with diversified economy and excellent schools. We are looking for the following:

DERMATOLOGY
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OB/GYN
NEUROLOGY
ORTHOPEDICS
PEDIATRICS
PODIATRY

Applicants must be BC/BE. Offering an excellent salary with an incentive arrangement and a competitive benefit package, leading to partnership after 18 months.

Reply with CV and references to:

Physician Recruitment
Eaton Medical Group
445 W. Eaton Ave
Tracy, CA 95376

MEMORIAL GENERAL HOSPITAL LAS CRUCES, NEW MEXICO

MODEL OB PRACTICE

Needs OB/GYN to join 2 obstetricians and 3 certified nurses to provide OB/GYN services to the underprivileged women of the area.

286 beds • Acute care facility with level II nursery • Excellent pediatric support • Nestled between the beautiful Rio Grande Valley and the majestic Organ Mountains • World class skiing • Water sports • Beautiful weather • Located in a university town • Named one of the top ten fastest growing cities in the country

Prefer BE/BC practitioner with ultrasound, colposcopy, high risk obstetrical experience. Salary, malpractice, benefits.

Please call: (505) 521-2258

(Continued on Page 204)

THE PERMANENTE MEDICAL GROUP NORTHERN CALIFORNIA

QUALITY

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REWARDS

The Permanente Medical Group, the largest multispecialty group practice in the U.S., is undergoing explosive growth in its Northern California region: the San Francisco Bay Area, Sacramento and the Central Valley. Our rapid increase in membership has created practice opportunities throughout the region.

Our physician-managed group is part of the comprehensive Kaiser Permanente Medical Care Program. As a TPMG physician, you have access to the latest medical technology and resources, the support of colleagues in all subspecialties — and the opportunity to provide excellent health care without the burdens of managing a practice.

TPMG offers many benefits: scheduled time off with cross-coverage provided by your colleagues, continuing education, malpractice insurance, a substantial retirement program and special arrangements for physicians transferring from established practice. For complete information, call or send CV to: The Permanente Medical Group, Inc., Richmond Prescott, M.D., Physician Recruitment Services, Dept. WJM-7153, 1814 Franklin, 4th Floor, Oakland, CA 94612. (800) 777-4912. EOE

KAISER PERMANENTE
Good People. Good Medicine.

(Continued from Page 203)

PHYSICIANS WANTED

OB/GYN, SAN FRANCISCO BAY AREA. Busy, well respected OB/GYN in growing, affordable suburban area seeks BE/BC associate. Perinatology training and/or interest in infertility a plus. Two offices on hospital campuses in Livermore and Pleasanton, supported by well-trained staff (including nurse and practitioner) and in-office ultrasound. Competitive salary first year with benefits and bonus, then eligible for partnership. Send CV to Sandra Colville, ValleyCare Health System, 4637 Chabot Dr, Ste 304, Pleasanton, CA 94588; (415) 373-4109.

THE STATE DEPARTMENT OF REHABILITATION needs a part-time Medical Consultant to work approximately 18 hours per week in Yuba City, Woodland, Grass Valley, Placerville, Auburn, Redding, and Yreka. Rate of pay is $32 to $40 per hour. For more information please contact Ron Golden, 470 Rio Lindo Ave, Ste 4, Chico, CA 95926; (916) 895-6047. An Affirmative Action Employer.

ASSOCIATE IN PEDIATRICS. Kern Medical Center, Bakersfield, California, a teaching hospital affiliated with UCLA and UCI Schools of Medicine, seeks an Associate in the Division of Pediatrics. Prerequisites include eligibility or certification by the American Board of Pediatrics, strong interest in teaching and qualifications for faculty appointment in UCLA Department of Pediatrics. Comprehensive salary and benefit package. A part-time private practice is permitted. Medical center is in central California, a mid-sized urban community with moderate cost of living. Send CV and inquiries to Navin Amin, MD, Chairman, Dept of Family Practice/Pediatrics, Kern Medical Center, 1830 Flower St, Bakersfield, CA 93305.

SOUTHERN CALIFORNIA. 39,000 visit Emergency Department in new hospital in San Bernardino. Base station and separate fast track with opportunity to teach. Opening for director and career Emergency Physicians at $90 per hour. Chance to join prestigious, democratic, academically oriented emergency group with excellent benefits. Contact Art Wong, MD, FACEP. Emergency Physicians Medical Group, 120 Montgomery St, San Francisco, CA 94104; (415) 989-1242.

PHYSICIANS, REGISTERED PHYSICAL THERAPISTS NEEDED IN CALIFORNIA AND NEVADA

Currently seeking California and Nevada state licensed BC/BE physicians specializing in Orthopedic Surgery, Neurology, and Internal Medicine to perform Workers' Compensation and personal injury evaluation and treatment in our California and Nevada offices.

We are also seeking a registered physical therapist to oversee all facilities in our company. We offer:

- Full-time or part-time
- Flexible hours
- Guaranteed income
- Possible expense for relocation
- Will provide training
- Excellent growth potential

Contact with CV:

800 N. Ben Maddox Way
#2225
Visalia, CA 93291
or call 1 (800) 347-2821
(ask for Jack or Shirl)

PHYSICIANS WANTED

SOUTHERN CALIFORNIA

Specialists and Primary Care Physicians—CIGNA Healthplans invites you to join our innovative and dynamic managed health care team. Our multidisciplinary HMO practice provides a supportive and collegial work environment at 31 locations. You will enjoy a wealth of cultural and recreational activities, access to major academic centers, and an excellent compensation package. *Call collect* **(818) 500-6570** *or send CV to* **Robert Harrington, MD, Professional Recruitment, CIGNA Healthplans of California, 505 N. Brand Blvd, Ste 400-49, Glendale, CA 91203.**

LONG BEACH—INTERNAL MEDICINE. BC/BE Internist to join four other Internists in busy primary care practice. Excellent office, lab, x-ray, and support services. Excellent benefits. Send CV to Number 190, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PSYCHIATRIST. Innovative team working with older adults. Med evaluations, consultations. Some supervision. $78K to $104K plus benefits for full-time. Part-time also available. Denver. National Institute for Behavior Change, (303) 296-2244. Ask for Lois Munson.

OB DIRECTOR for a Family Practice residency program. Duties include teaching, performing cesarean sections and gynecological surgery. Some private patients. Salary of $120,000 a year plus malpractice insurance and bonus. Send CV to Ed Hughell, MD, Residency Director, 315 E. 13th St, Merced, CA 95340; or call (209) 385-7171.

SACRAMENTO, Internal Medicine or Family Practice. BC/BE with experience/training in Addiction Medicine. ASAM welcome. Kaiser Permanente has approximately 360,000 members in the Sacramento area. Active outpatient chemical dependency program. Hospital care for detox. No rehab. Dual diagnosis is handled by ourselves and psychiatry. At least 50 percent of time in addiction medicine with opportunity to evolve to full-time. Very attractive salary and full benefit package. Available in three months. Please contact David C. Meek, MD, Sub-chief, Alcohol and Drug Program, The Permanente Medical Group, Inc, 2025 Morse Ave, Sacramento, CA 95825; or call (916) 978-1495. EOE.

ARIZONA. VA Medical Center, Prescott, Arizona, Medical Service is recruiting for a full-time, BC Internal Medicine Physician. Position is available now. Prescott is a 217-bed general medical hospital with an active medical service, ICU/CCU, ambulatory care, rehabilitation medicine service, alcohol dependency treatment program, and intermediate bed care units. Prescott is located in the mountains of north-central Arizona with a population of 25,000. Salary range is $70,000 to $80,000 depending on qualifications. Send CV to F. C. Lepperd, Jr, MD, Chief of Staff, VA Medical Center, Prescott, AZ 86313; or call (602) 445-4860, ext 301. Equal Opportunity Employer.

LAYTON, UTAH—FAMILY PHYSICIANS. Associate needed to join young, BC Family Physician in newly opened office. Layton is 12 miles south of Ogden and 15 miles north of Salt Lake City. For more information, send your CV to Manager, Professional Relations, Humana Inc, Dept HH-2B, 500 W. Main St, Louisville, KY 40201-1438; or call toll-free 1 (800) 626-1590.

PEDIATRICIAN, BE/BC. Join established two Pediatrician practice. Monterey Bay area of California. Salaried position with partnership opportunity. Excellent benefits, office located adjacent to modern 250-bed hospital. Community of 100,000 plus population. Call rotation divided among six Pediatricians. CV to Number 188, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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OUTSTANDING SOUTHWEST OPPORTUNITY

BC Family Practice Physician seeking second or third physician Family Practitioner (or Internist) in one of the fastest growing areas of US. The practice is situated in a new medical office building on the campus of modern, progressive Northwest Hospital in suburban northwest Tucson.

Substantial fee-for-service opportunity in this beautiful southwestern community 40 minutes from skiing, four and one-half hours from Mexico beaches. Excellent call coverage schedule and financial package. Contact **Physician Recruiter, Northwest Hospital Administration, 6200 N. La Cholla Blvd, Tucson, AZ 85741; (602) 742-9000, ext. 100.**

RADIOLOGIST—SAN FRANCISCO. Opening for BC Diagnostic Radiologist at Mount Zion Hospital in San Francisco. MR, angiography, CT, ultrasound, general diagnosis. Please contact P. Brodey, MD, 1600 Divisadero St, San Francisco, CA 94115; (415) 885-7466.

FAMILY PRACTITIONER. Beautiful central valley community clinic offers opportunity for Family Practitioner to include Obstetrics in his or her practice. Spanish language capability preferred. High compensation, excellent working conditions. Contact Jim Ellis, Western Physicians Registry, 710 Van Ness Ave, San Francisco, CA 94102; 1 (800) 437-7676.

UNIQUE CLINICAL INTERNAL MEDICINE FELLOWSHIP. UCLA Department of Medicine offering fourth year training in Internal Medicine, through the Kennamer Fellowship, supported by the Albert Parvin Foundation. Fellowship begins July 1, 1991 for candidates BC/BE in Internal Medicine. A one year fellowship for practice careers. One fellow will be based at each of UCLA's major affiliates: Cedars-Sinai, Harbor, UCLA-San Fernando Valley, UCLA and Wadsworth/VA. Stipend $28,500 plus health insurance and worker's compensation. For forms and details write Roy T. Young, MD, UCLA Dept of Medicine, 32-115 CHS, 10833 Le Conte Blvd, Los Angeles, CA 90024. Applications deadline March 30, 1990. Interviews by invitation. All applicants notified before July 1, 1990. Equal Opportunity/Affirmative Action Employer.

SEEKING A PHYSICIAN to associate with a Family Practice group. Ultramodern facility with outpatient surgical suite. Located in Corona, California, between Orange County and San Diego. Growing area. Good climate. We are offering an association with excellent economic advantage. Contact Ann Holmes, (714) 734-3042.

(Continued on Page 206)

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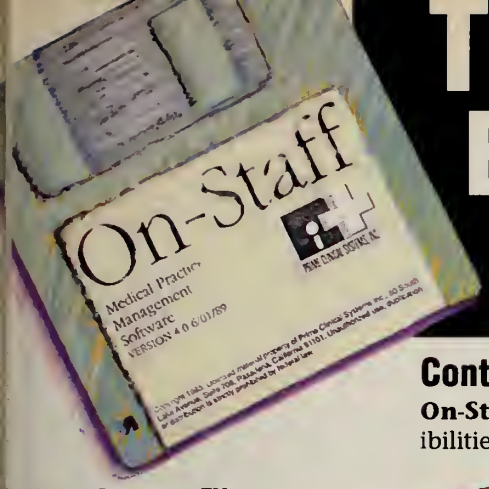

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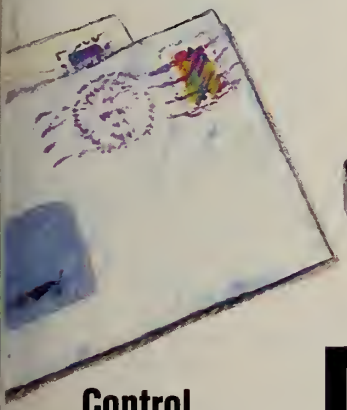

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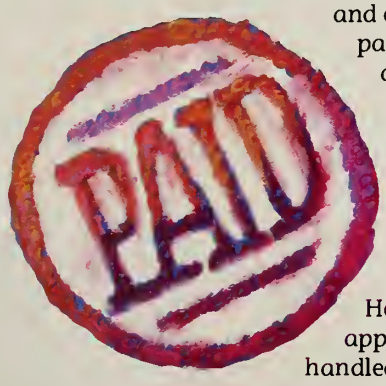
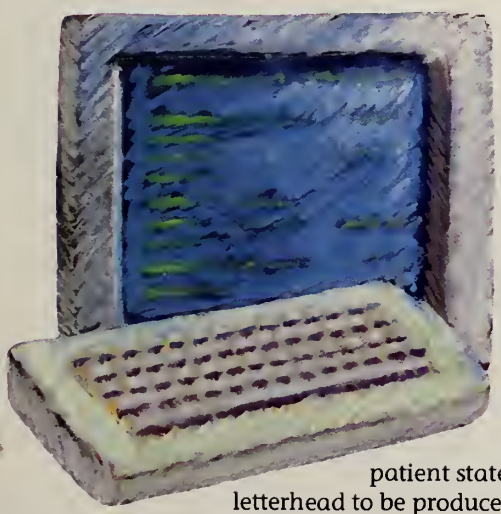
On-Staff computes the financial responsibilities of insurance carriers versus patients, and effectively monitors payments and adjustments. The system is specifically designed to speed the collection process. **On-Staff** automates not just billing, but also the whole range of follow-up routines. Hence, insurance tracers, appeal letters, etc. are all handled automatically.





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(Continued from Page 204)

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IMMEDIATE OPENING. University affiliated ambulatory center. Full-time position available immediately in San Bernardino/Riverside, California. Competitive basic salary guarantee plus attractive fringe benefits. Contact Daniel Injo, MD, 22182 Barton Rd, Grand Terrace, CA 92324; (714) 370-1300.

URGENT CARE PHYSICIAN. Full- or part-time position available for northern California urgent care clinic. Contact David Lyons, MD, 900 Oro Dam Blvd, Oroville, CA 95991; (916) 534-9183.

PRACTICES AVAILABLE

SOUTHERN CALIFORNIA. Unusual opportunity to take over established orthopedic (medical-legal) practices in east Los Angeles County and/or Orange County. Negotiable terms. (714) 734-3048 or reply to G. Rothman, 417 Associated Rd, A-255, Brea, CA 92621.

BEAUTIFUL NAPA VALLEY, CALIFORNIA. Solo Psychiatric practice. Good clientele. Potential for growth as desired. Physician retiring. Residence available. Call David Lucchesi, (707) 552-3831.

WELL ESTABLISHED GENERAL INTERNIST'S PRACTICE. Excellent coverage and income. Silicon Valley. Physician will retire incrementally. U.S. trained BE/BC only, please. Reply to Number 178, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

CALIFORNIA. Sunny, warm southern California resort town, Palm Springs area. Long established. Practice suitable for Internal Medicine or Family Practice. Two hospitals. Reason: retiring. Great potential and golf! Reply to Number 181, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

FAMILY PRACTICE. San Diego East County. Gross over $300,000. Beautifully decorated and well equipped. Practice Consultants, (619) 528-2321.

FOR SALE. Established, busy Urology practice in southwestern New Mexico. No investment required. Excellent year 'round climate and outdoor recreational opportunities. Call collect, Pierson Deming, MD, (505) 388-1561 (office) or (505) 388-4557 (home); or call Steve Jacobson, Administrator, Gila Regional Medical Center, (505) 388-1591.

PSYCHIATRY PRIVATE PRACTICE. San Diego desirable area, transferrable patient base and referral sources. Considerable capacity for growth. Gross averages $120,000 on half-time. Contact Practice Consultants, (619) 528-2321, Dr Bernard Press, Broker.

SAN DIEGO—CARDIOLOGY-INTERNAL-FAMILY-OB/GYN AND PEDIATRIC PRACTICES AVAILABLE. Long established—doctors retiring. Various prices and low down payments. Call CBI, San Diego's professional practice sales specialists, (619) 283-7009.

NORTHERN AND CENTRAL CALIFORNIA. Established practices available: Dermatology, Family, Geriatrics, Internal Medicine, OB/GYN, Ophthalmology, Pediatrics, Plastic Surgery, and Urology. Reasonable terms and prices. Call/write Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (415) 376-0762, FAX (415) 376-0813.

OB/GYN, Beach City. Doctor leaving state. $400K gross 1989. Asking $100K. Financing available for qualified buyer. N. Newton, (818) 445-0458.

GENERAL PRACTICE CLINIC FOR SALE. Established 25 years. Supports two physicians, physician assistant. X-ray and pharmacy on premises. Spanish helpful. Large hospitals nearby. California central valley near educational and recreational facilities. Ideal for family living. Reply to Number 189, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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Northern California, Carol Sweig and Jim Ellis, Directors, (415) 673-7676 or (800) 437-7676

Southern California, Tracy Zweig, Director, (818) 999-1050 or (800) 635-3175

BC RADIOLOGIST NEEDED—SAN FRANCISCO MR, basic angiography, general diagnosis. Long-term position possible. Contact P. Brodey, MD; (415) 885-7466.

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X-RAY—UNIVERSAL 300/125. 14 × 36 Bucky, automatic processor, accessories, cassettes 14 × 36 to 8 × 10, printer, view boxes, lead window, apron; (707) 526-7790.

FOR SALE one-and-a-half-year-old Photophone x-ray transmission unit. Excellent unit to transmit x-rays from hospital to home. Computer enhanced. Complete unit, transmitter and receiving unit which is portable with case. Sells new for $23,000. Will sell for $15,000 complete. Contact Ronald Kump, MD, 1644 E. Oaktree Terrace, Glendora, CA 91740; (818) 963-8907.

CLASSIFIED INFORMATION
(415) 541-0900, Ext 376

OFFICE SPACE

GROWTH AREA OF SANTA CLARA VALLEY. New medical office space for lease in the growth area of Silicon Valley, Morgan Hill, California. Easy access, abundant parking, well located, generous tenant improvement allowances. Excellent patient referral sources. Contact Dr Jon Hatakeyama, (408) 779-7391.

FULLY EQUIPPED FAMILY PRACTICE AVAILABLE IN POWAY, CALIFORNIA. Seven exam rooms that accommodate several physicians. Premises can be rented or real estate purchased. Call CBI, San Diego's professional practice sales specialists, (619) 283-7009.

PLACEMENT SERVICES

AT LAST! Western Practitioner Resources places nurse practitioners, physician assistants, and certified nurse midwives in your clinical setting. Please phone Heidi Bourne, Director, (800) 345-5859.

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Ad Council

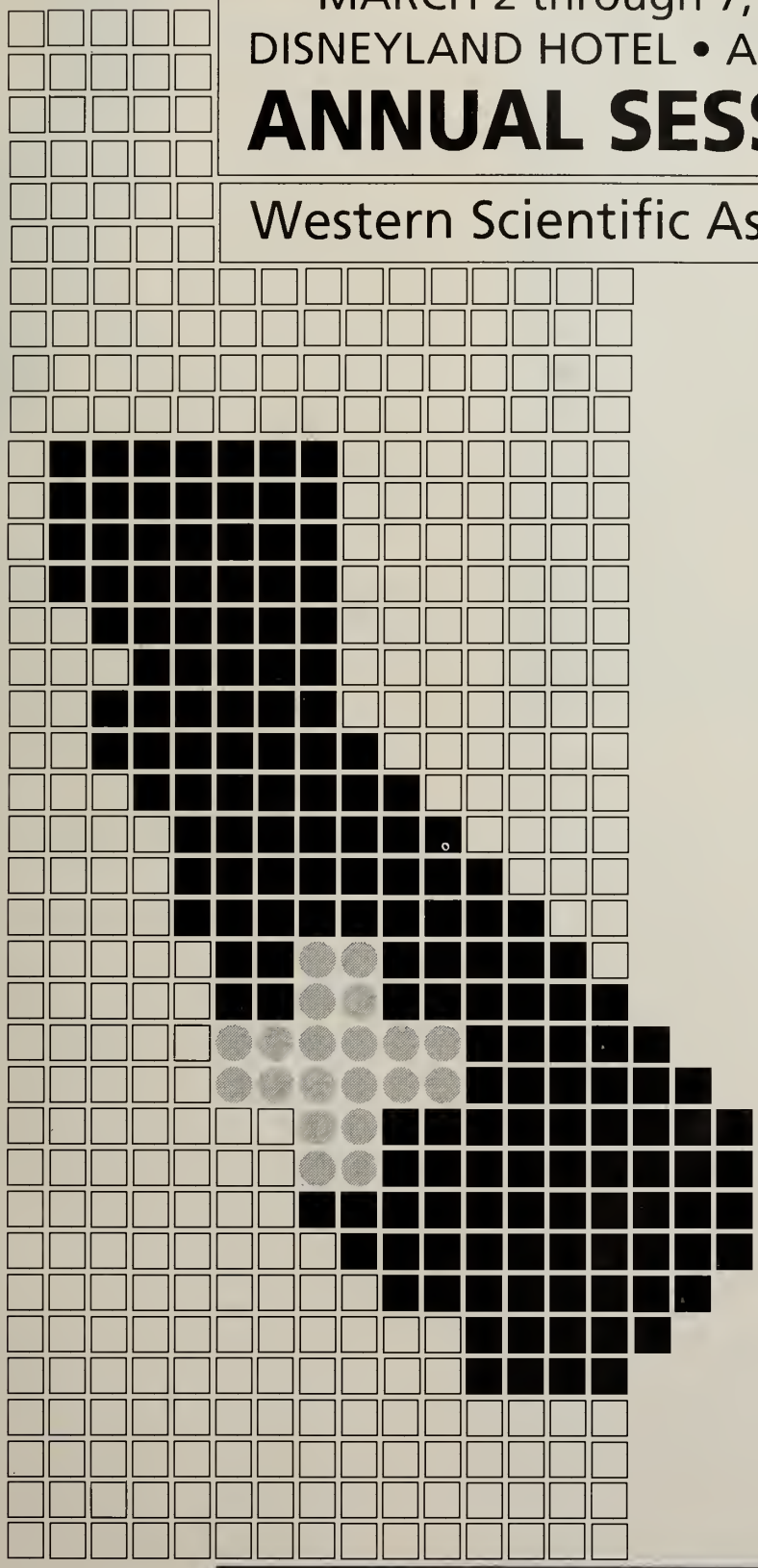
(Continued on Page 213)

CALIFORNIA MEDICAL ASSOCIATION

MARCH 2 through 7, 1990
DISNEYLAND HOTEL • ANAHEIM

ANNUAL SESSION

Western Scientific Assembly



SEE FOLLOWING PAGES FOR SCHEDULE

Friday, March 2

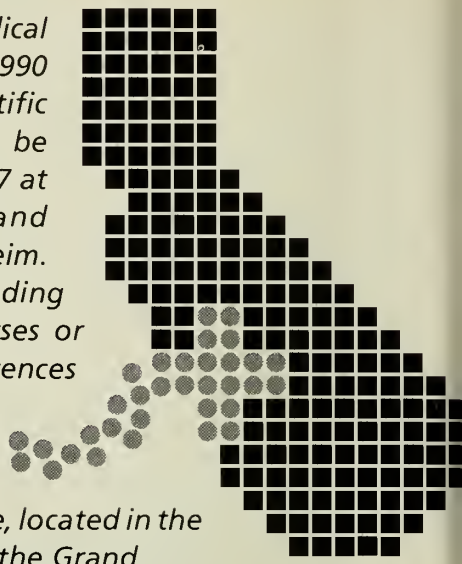
GOLDEN APPLE AWARD

William P. Longmire, Jr., MD, Professor Emeritus of Surgery at UCLA, has been selected by the Committee on Scientific Assemblies to receive CMA's 1990 Golden Apple Award. This award spotlights exceptional physicians who have made a lifelong commitment to teaching and are renowned for their charismatic, scientific and educational talents. Doctor Longmire is a member of the President's Cancer Panel and the National Cancer Advisory Board, and served as Chairman of the Department of Surgery at UCLA from 1948 until 1976.

The award will be presented following Doctor Longmire's presentation, "Can A Clinician Be a Scientist?" All are invited to attend. Come hear an outstanding teacher address a subject of interest to all physicians.

Can A Clinician Be a Scientist?

Friday, March 2, 12:15 pm
Disneyland Hotel



California Medical Association's 1990 Western Scientific Assembly will be held March 2-7 at the Disneyland Hotel in Anaheim. Persons attending scientific courses or special conferences are asked to register on site in the Center Lounge, located in the foyer outside the Grand Ballroom of the Disneyland Hotel.

For more information on the following programs, please contact Sheri Sylvia at CMA, (415) 882-5184.

Thursday, March 1

01 Basic Cardiac Life Support

Friday, March 2

02 Medical Staff Issues: 1990

03 Advanced Cardiac Life Support Certification Program

04 Therapy in Neurology and Infectious Problems in the Elderly

05 Sports Medicine - Shoulder, Knee and Ankle and Foot Injuries

06 Reproductive Hazards in the Workplace

07 Managing HIV Infection in 1990

08 Asthma— Current Concepts

09 Golden Apple Award Presentation

10 Emergency Medicine on the Front Line 1990 - Expect the Unexpected

11 The New Epidemics: Pediatrics for the 90s

12 Prenatal Influences in the Outcome of Pregnancy

13 Can We Talk?

Saturday, March 3

14 Advanced Cardiac Life Support Recertification Course

15 Allergy and the Skin: What's New and Clinically Important

16 Selected Topics in Family Practice

17 Serious Diseases With Benign Symptoms: Some Great Pretenders

18 Suture Course

19 The Crack Cocaine Epidemic: Its Impact on the Health Care System

20 Addiction and the Family

21 Eye Care in the 1990s

22 Major Dysfunctions in the Life Cycle

23 Sedation and Patient Safety in Your Practice

24 Sun vs Skin: Skin Malignancies and Aging

25 Treatment of Disorders of the Thyroid and Parathyroid Glands

26 The Knee: A Comprehensive Review of Diagnostic and Treatment Entities

27 Planning for Retirement and a Stable Financial Future

Sunday, March 4

28 Reproductive and Urological Problems in the Family

29 Difficult Wound Problems and Their Management

30 Pediatric and Adult Head and Neck Surgery-Otolaryngology: Update 1990

31 Lasers, Lithotripsy and Like Therapy

32 Leave Your Butts Behind: The NCI Guide to Physician Intervention in Smoking Cessation

33 Cytology: Answering the Questions Patients and Physicians Ask

34 SECRETS: Talking to Teens About AIDS

35 Keynote Speaker

36 All In A Day's Work? A Workshop on Violence in the Health Care Setting

37 The Perfect Match: A Workshop on Residency Selection and Career Planning

38 A Critical Look at the Washington Scene

39 Physicians and the Law

Sunday, March 4

WESTERN SCIENTIFIC ASSEMBLY KEYNOTE SPEAKER

William Y. Rial, MD, is currently Director of Provider Relations for the Blue Cross and Blue Shield Association and is a visiting lecturer at Northwestern University Medical School, both of which are located in Chicago, Illinois.

Doctor Rial has been with the Blue Cross/Blue Shield Association since 1985, before which time he practiced as a family physician in Pennsylvania for 34 years. He has held numerous leadership positions within organized medicine at the state and national levels. From his unique experience within medicine and the insurance industry, Doctor Rial will explore the future of private practice in the coming decade and suggest how physicians can cope with the radical economic changes now evolving.

Strategies For Private Practice in the 90s

Sunday, March 4, 12:15 pm
Disneyland Hotel

CONCURRENT EVENTS

HOUSE OF DELEGATES

The CMA House of Delegates meets Saturday, March 3 through Wednesday, March 7 at the Disneyland Hotel. Sit in on reference committee hearings and House sessions to see firsthand how CMA policies are shaped. Highlights of this year's House will be the farewell address of out-going CMA President Dr. William G. Plested, a Los Angeles cardiovascular surgeon, and the inaugural address of CMA's President-Elect, Dr. Charles W. Plows, an Anaheim obstetrician. Registration will be available March 2-7 at the Disneyland Hotel.

CMA YOUNG PHYSICIAN'S SECTION ANNUAL ASSEMBLY

The first assembly of CMA's newly formed Young Physician's Section will be held Saturday, March 3 at the Disneyland Hotel. YPS will host a reception, sponsored by SCPIE, which is open to all CMA members after the Assembly, which ends at 5:30 pm.

SPECIAL EVENTS

A variety of events will take place this year. Registrations can be made at the Special Events Booth in the Disneyland Hotel.

- J. Paul Getty Museum/Santa Monica Tour
- Newport Harbor Cruise and Dinner
- Every Cloud Has a Silver Lining
- Laguna Impressions and High Tea at the Ritz Carlton

EXHIBITS

The exhibit hall offers something for everyone: pharmaceutical displays, computer and office systems, medical testing systems, insurance, investment opportunities, and much more. Prizes!

GENERAL INFORMATION

LOCATION

The CMA 1990 Western Scientific Assembly will be held at the Disneyland Hotel, 1150 West Cerritos Avenue, Anaheim, CA 92802. Call (714) 778-6600 for hotel reservation information.

FEES

There is no general registration fee for CMA members, fellows, residents, interns, and medical students, nor to their nonphysician guests who do not attend educational programs.

Non-member physicians are required to pay a $300 general registration fee; nurses and allied health personnel are required to pay a $50 fee.

REGISTRATION

Advance registration closes February 9, 1990. Attendees may register on site at the Disneyland Hotel's Center Lounge. Registration will be open:

Thursday, March 1	1:00 pm to 5:00 pm
Friday, March 2	7:30 am to 5:00 pm
Saturday, March 3	7:00 am to 5:00 pm
Sunday, March 4	7:30 am to 5:00 pm

The registration desk will move to the House registration area outside the Marina Ballroom:

Monday, March 5	9:00 am to 4:00 pm
Tuesday, March 6	9:00 am to 4:00 pm
Wednesday, March 7	9:00 am to 12:00 pm

ANY QUESTIONS?

Contact CMA, Western Scientific Assembly,
(415) 882-5184.

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Internists and Cardiologist (BC/BE) - Join us in our high quality, expanding, 25 member Department of Medicine where you will benefit from our university affiliated internal medicine residency program. Faculty appointment available. This East Bay suburban setting has excellent schools, and is only 25 miles from San Francisco. Please send CV, or contact Michael Melewicz, M.D., Dept. of Medicine, The Permanente Medical Group, Inc., 200 Muir Road, Martinez, CA 94553. (415) 372-1069.

ROSEVILLE

General Internists (BC/BE) — Immediate openings for California licensed Internists at our Roseville facility, 90 miles from San Francisco or Sierra skiing & camping. University associated residency program. Send CV to: Tony Cantelmi, M.D., The Permanente Medical Group, Inc., 1001 Riverside Blvd., Roseville, CA 95678.

SAN JOSE

Family Practitioner (BC/BE) — Our 228-bed Santa Teresa Medical Center serves 128,000 members. Predominately outpatient practice located in Silicon Valley, approximately 45 minutes south of San Francisco and 30 minutes from the Pacific Coast. Send CV to D. Bardole, The Permanente Medical Group, Inc., 260 International Circle, San Jose, CA 95119.

Surgeons (BC/BE) - One General Surgeon and one Surgeon to do both general and vascular surgery. We are a 9 surgeon department with modern offices adjacent to the 228-bed hospital equipped with 7 operating rooms. We handle a full range of general, thoracic, vascular and plastic surgery cases, and our group includes about 100 fully trained physicians in all specialties. Please apply to the Oakland address below.

SOUTH SAN FRANCISCO

Seeking highly-motivated **BC/BE Internists and a BC/BE Gastroenterologist-Internist** for this expanding practice adjacent to our 125-bed community hospital. Send CV to: Mark Cole, M.D., Dept. of Medicine, The Permanente Medical Group, Inc., 1200 El Camino Real, So. San Francisco, CA 94080.

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Excellent opportunity for **BC/BE Family Practitioner** to join a growing department. Multispecialty clinic emphasizing personalized care. Full hospital privileges including ICU/CCU, but no Obstetrics. Very favorable call schedule. Forward CV to: Steven Freedman, M.D., The Permanente Medical Group, Inc., 1550 Gateway Blvd., Fairfield, CA 94533. (707) 427-4260.

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To inquire about other openings with our successful, growing medical group, send CV to: Richmond Prescott, M.D., Physician Recruitment Services, Dept. WJM-5114, The Permanente Medical Group, Inc., 1814 Franklin, 4th Floor, Oakland, CA 94612. (415) 987-4949. EOE

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(Continued from Page 206)

SYMPOSIUM

6TH ANNUAL SIERRA ARTHRITIS SYMPOSIUM to be held in Yosemite, California, at the Ahwahnee Hotel, March 31 and April 1, 1990. For more information contact Gloria Fitzgerald, Community Hospitals of Central California, (209) 442-3936.

MEETINGS

ADVANCED ECHOCARDIOGRAPHY AND DOPPLER ULTRASOUND 1990

June 13-16, 1990. San Diego, California. Fees: $455 for ACC members; $495 for non-members; $395 for fellows-in-training, nurses, and technicians. 23.5 Category 1 credit hours. For information, call **American College of Cardiology, (800) 253-4636; in Maryland, (301) 897-5400.**

FAMILY PRACTICE DAY
MARCH 8, 1990
7:30 A.M. - 5:00 P.M.
SWEDISH HOSPITAL MEDICAL CENTER
GLASER AUDITORIUM
(206) 386-2265

41st ANNUAL MEETING—SPOKANE SOCIETY OF INTERNAL MEDICINE

March 9, 10, 1990. "Advances in Clinical Cardiology." National faculty, nine hours CME, Ridpath Hotel, Spokane, Washington. Cost: Physician/Nonmember—$75; Physician/Member—$50; Associated Professionals—$50; Residents—$10. Contact **Linda Browne, PO Box 8443, Spokane, WA 99203; (509) 448-2513.**

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California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 2-7, 1990, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 13-16, 1990, Keystone.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 12-14, 1990, Ilikai, Honolulu.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 26-28, 1990, Sun Valley.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 4-6, 1990, Sheraton, Billings.

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Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 12-14, 1990, Marriott Hotel, Salt Lake City.

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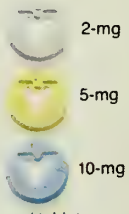

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Warnings: *Angioedema* Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including VASOTEC In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms Angioedema associated with laryngeal edema may be fatal **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered.** (See ADVERSE REACTIONS)

Hypotension Excessive hypotension is rare in uncomplicated hypertensive patients treated with VASOTEC alone Patients with heart failure given VASOTEC commonly have some reduction in blood pressure, especially with the first dose, but discontinuation of therapy for continuing symptomatic hypotension usually is not necessary when dosing instructions are followed; caution should be observed when initiating therapy (See DOSAGE AND ADMINISTRATION) Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death, include those with the following conditions or characteristics heart failure, hyponatremia, high-dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology It may be advisable to eliminate the diuretic (except in patients with heart failure), reduce the diuretic dose, or increase salt intake cautiously before initiating therapy with VASOTEC in patients at risk for excessive hypotension who are able to tolerate such adjustments (See PRECAUTIONS, *Drug Interactions* and ADVERSE REACTIONS) In patients at risk for excessive hypotension, therapy should be started under very close medical supervision and such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased Similar considerations may apply to patients with ischemic heart disease or cardiovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline A transient hypotensive response is not a contraindication to further doses of VASOTEC, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of VASOTEC or concomitant diuretic may be necessary

Neutropenia/Agranulocytosis Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered

Precautions: *General Impaired Renal Function* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis increases in blood urea nitrogen and serum creatinine were observed in 20% of patients These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy In such patients, renal function should be monitored during the first few weeks of therapy

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment Dosage reduction and/or discontinuation of the diuretic and/or VASOTEC may be required

Evaluation of patients with hypertension or heart failure should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hyperkalemia. Elevated serum potassium (>5 7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials In most cases these were isolated values which resolved despite continued therapy Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients In clinical trials in heart failure, hyperkalemia was observed in 3 8% of patients, but was not a cause for discontinuation

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with VASOTEC (See *Drug Interactions.*)

Surgery/Anesthesia In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion

Information for Patients

Angioedema Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician

Hypotension Patients should be cautioned to report lightheadedness, especially during the first few days of therapy If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure, patients should be advised to consult with the physician

Hyperkalemia. Patients should be told not to use salt substitutes containing potassium without consulting their physician

Neutropenia Patients should be told to report promptly any indication of infection (e g , sore throat, fever) which may be a sign of neutropenia

NOTE As with many other drugs, certain advice to patients being treated with enalapril is warranted This information is intended to aid in the safe and effective use of this medication It is not a disclosure of all possible adverse or intended effects.

Drug Interactions

Hypotension. Patients on Diuretic Therapy Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril It it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION)

Agents Causing Renin Release The antihypertensive effect of VASOTEC is augmented by antihypertensive agents that cause renin release (e g , diuretics)

Other Cardiovascular Agents VASOTEC has been used concomitantly with beta-adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine prazosin, and digoxin without evidence of clinically significant adverse interactions

Agents Increasing Serum Potassium VASOTEC attenuates potassium loss caused by thiazide-type diuretics Potassium-sparing diuretics (e g , spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium Potassium-sparing agents should generally not be used in patients with heart failure receiving VASOTEC

Lithium Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors A few cases of lithium toxicity have been reported in patients receiving concomitant VASOTEC and lithium and were reversible upon discontinuation of both drugs It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium

Pregnancy – Category C. There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose) Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril but did not occur when these animals were supplemented with saline Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose).

Radioactivity was found to cross the placenta following administration of labeled enalapril to pregnant hamsters

There are no adequate and well-controlled studies of enalapril in pregnant women However, data are available that show enalapril crosses the human placenta Because the risk of fetal toxicity with the use of ACE inhibitors has not been clearly defined, VASOTEC® (Enalapril Maleate, MSD) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Postmarketing experience with all ACE inhibitors thus far suggests the following with regard to pregnancy outcome Inadvertent exposure limited to the first trimester of pregnancy has not been reported to affect fetal outcome adversely Fetal exposure during the second and third trimesters of pregnancy has been associated with fetal and neonatal morbidity and mortality

When ACE inhibitors are used during the later stages of pregnancy there have been reports of hypotension and decreased renal perfusion in the newborn Oligohydramnios in the mother has also been reported, presumably representing decreased renal function in the fetus Infants exposed *in utero* to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion with the administration of fluids and pressors as appropriate Problems associated with prematurity such as patent ductus arteriosus have occurred in association with maternal use of ACE inhibitors, but it is not clear whether they are related to ACE inhibition, maternal hypertension, or the underlying prematurity

Nursing Mothers Milk in lactating rats contains radioactivity following administration of ^{14}C enalapril maleate It is not known whether this drug is secreted in human milk Because many drugs are secreted in human milk caution should be exercised when VASOTEC is given to a nursing mother

Pediatric Use Safety and effectiveness in children have not been established

Adverse Reactions: VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2987 patients

HYPERTENSION The most frequent clinical adverse experiences in controlled trials were headache (5 2%), dizziness (4 3%), and fatigue (3%)

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were diarrhea (1 4%), nausea (1 4%), rash (1 4%), cough (1 3%), orthostatic effects (1 2%), and asthenia (1 1%)

HEART FAILURE The most frequent clinical adverse experiences in both controlled and uncontrolled trials were dizziness (7 9%), hypotension (6 7%), orthostatic effects (2 2%), syncope (2 2%), cough (2 2%), chest pain (2 1%), and diarrhea (2 1%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in both controlled and uncontrolled clinical trials were fatigue (1 8%), headache (1 8%), abdominal pain (1 6%), asthenia (1 6%) orthostatic hypotension (1 6%), vertigo (1 6%), angina pectoris (1 5%), nausea (1 3%), vomiting (1 3%), bronchitis (1 3%) dyspnea (1.3%), urinary tract infection (1 3%), rash (1 3%), and myocardial infarction (1 2%)

Other serious clinical adverse experiences occurring since the drug was marketed or adverse experiences occurring in 0 5% to 1% of patients with hypertension or heart failure in clinical trials in order of decreasing severity within each category

Cardiovascular. Cardiac arrest, myocardial infarction or cerebrovascular accident possibly secondary to excessive hypotension in high-risk patients (see WARNINGS, *Hypotension*), cardiac arrest, pulmonary embolism and infarction, rhythm disturbances, atrial fibrillation, palpitation

Digestive Ileus, pancreatitis, hepatitis or cholestatic jaundice, melena, anorexia, dyspepsia constipation, glossitis, stomatitis

Musculoskeletal Muscle cramps

Nervous/Psychiatric Depression, confusion, ataxia, somnolence, insomnia, nervousness, paresthesia

Urogenital Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION)

Respiratory Bronchospasm, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection

Skin Herpes zoster, urticaria, pruritus, alopecia, flushing, hyperhidrosis

Special Senses Blurred vision, taste alteration, tinnitus.

A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgias/arthritis, myalgias, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity rash, and other dermatologic manifestations

Angioedema Angioedema has been reported in patients receiving VASOTEC (0.2%) Angioedema associated with laryngeal edema may be fatal If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately (See WARNINGS)

Hypotension In the hypertensive patients, hypotension occurred in 0 9% and syncope occurred in 0.5% of patients following the initial dose or during extended therapy Hypotension or syncope was a cause for discontinuation of therapy in 0 1% of hypertensive patients In heart failure patients, hypotension occurred in 6 7% and syncope occurred in 2 2% of patients Hypotension or syncope was a cause for discontinuation of therapy in 1 9% of patients with heart failure (See WARNINGS)

Clinical Laboratory Test Findings

Serum Electrolytes Hyperkalemia (see PRECAUTIONS), hyponatremia

Creatinine, Blood Urea Nitrogen In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0 2% of patients with essential hypertension treated with VASOTEC alone Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis (See PRECAUTIONS) In patients with heart failure who were also receiving diuretics with or without digitalis, increases in blood urea nitrogen or serum creatinine, usually reversible upon discontinuation of VASOTEC and/or other concomitant diuretic therapy, were observed in about 11% of patients Increases in blood urea nitrogen or creatinine were a cause for discontinuation in 1 2% of patients

Hemoglobin and Hematocrit Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0 3 g% and 1 0 vol %, respectively) occur frequently in either hypertension or heart failure patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists In clinical trials, less than 0 1% of patients discontinued therapy due to anemia

Other (Causal Relationship Unknown) In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported A few cases of hemolysis have been reported in patients with G6PD deficiency

Liver Function Tests Elevations of liver enzymes and/or serum bilirubin have occurred

Dosage and Administration: *Hypertension* In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC The diuretic should, if possible, be discontinued for two to three days before beginning therapy with VASOTEC to reduce the likelihood of hypotension (See WARNINGS.) If the patient's blood pressure is not controlled with VASOTEC alone, diuretic therapy may be resumed

If the diuretic cannot be discontinued, an initial dose of 2 5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour (See WARNINGS and PRECAUTIONS, *Drug Interactions*)

The recommended initial dose in patients not on diuretics is 5 mg once a day Dosage should be adjusted according to blood pressure response The usual dosage range is 10 to 40 mg per day administered in a single dose or in two divided doses In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval In such patients, an increase in dosage or twice-daily administration should be considered If blood pressure is not controlled with VASOTEC alone, a diuretic may be added

Concomitant administration of VASOTEC with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS)

Dosage Adjustment in Hypertensive Patients with Renal Impairment The usual dose of enalapril is recommended for patients with a creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL) For patients with creatinine clearance ≤ 30 mL/min (serum creatinine ≥ 3 mg/dL), the first dose is 2 5 mg once daily The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily

Heart Failure VASOTEC is indicated as adjunctive therapy with diuretics and digitalis The recommended starting dose is 2.5 mg once or twice daily After the initial dose of VASOTEC, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour (See WARNINGS and PRECAUTIONS, *Drug Interactions*) If possible, the dose of the diuretic should be reduced, which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of VASOTEC does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension The usual therapeutic dosing range for the treatment of heart failure is 5 to 20 mg daily given in two divided doses The maximum daily dose is 40 mg Once-daily dosing has been effective in a controlled study, but nearly all patients in this study were given 40 mg, the maximum recommended daily dose, and there has been much more experience with twice-daily dosing In addition, in a placebo-controlled study which demonstrated reduced mortality in patients with severe heart failure (NYHA Class IV), patients were treated with 2 5 to 40 mg per day of VASOTEC, almost always administered in two divided doses (See CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects.*) Dosage may be adjusted depending upon clinical or hemodynamic response (See WARNINGS)

Dosage Adjustment in Patients with Heart Failure and Renal Impairment or Hyponatremia In patients with heart failure who have hyponatremia (serum sodium < 130 mEq/L) or with serum creatinine >1 6 mg/dL, therapy should be initiated at 2 5 mg daily under close medical supervision (See DOSAGE AND ADMINISTRATION, *Heart Failure,* WARNINGS, and PRECAUTIONS, *Drug Interactions.*) The dose may be increased to 2 5 mg b i d., then 5 mg b.i.d and higher as needed, usually at intervals of four days or more, if at the time of dosage adjustment there is not excessive hypotension or significant deterioration of renal function The maximum daily dose is 40 mg

For more detailed information, consult your MSD Representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486 J9VS54R2(818)

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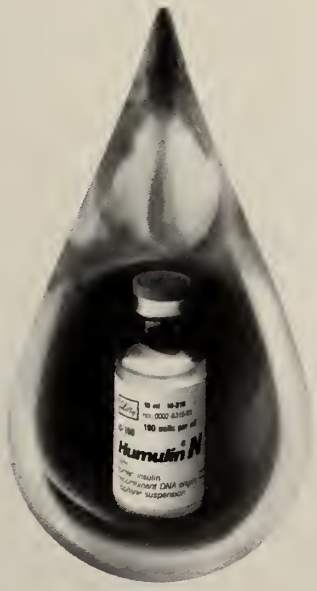

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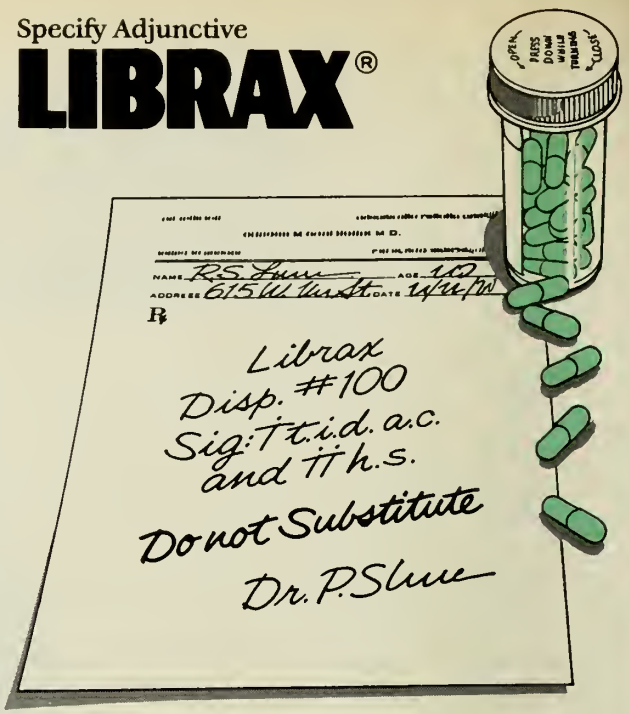

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium bromide.

Please consult complete prescribing information, a summary of which follows:

* Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).
Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.
As with all anticholinergics, inhibition of lactation may occur.
Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).
Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.
Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.
Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of chlordiazepoxide; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. After extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

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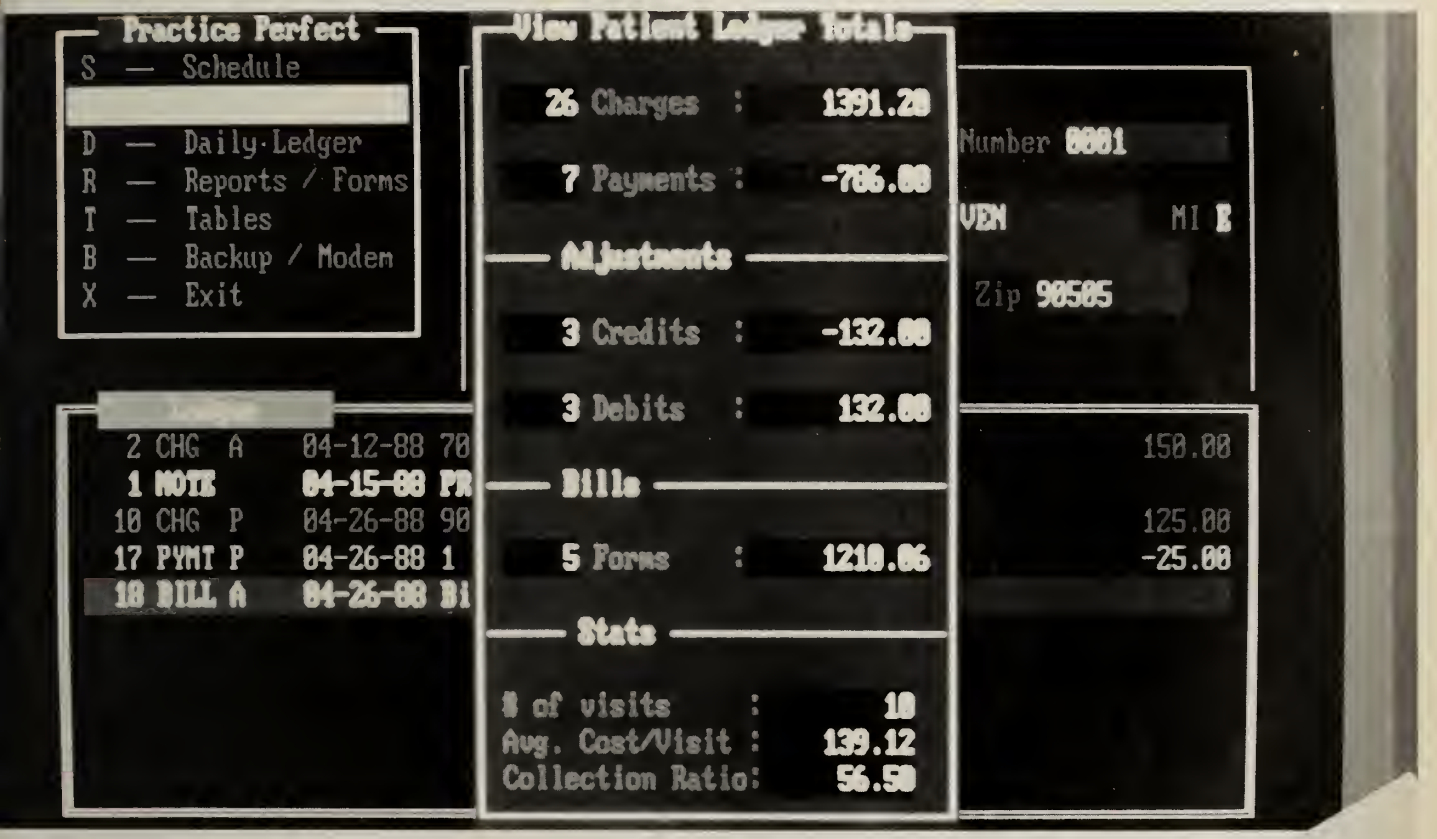

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$$\frac{240}{<35}$$

What's a common denominator of most heart attack victims?

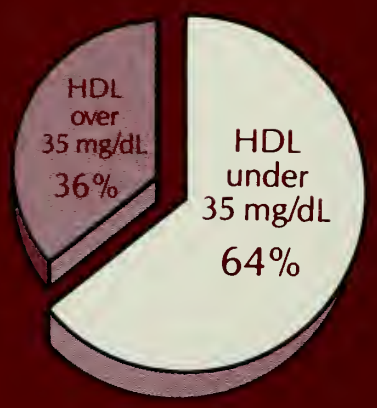
HDL

<35

mg/dL

Mixed hyperlipidemias—elevated cholesterol *and* triglycerides—are common among heart attack victims,[1] and nearly two-thirds of people who developed myocardial infarction in the PROCAM Trial had a low (<35 mg/dL) baseline level of HDL cholesterol.[2]

HEART ATTACK PATIENTS
(PROCAM TRIAL)[2]



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A powerful case for

LOPID® (gemfibrozil)

BID 600-mg Tablets

Raised low HDL 25%

—in patients whose baseline HDL was below 35 mg/dL in the landmark Helsinki Heart Study (HHS).[3]

Reduced heart attack incidence* up to 62%

—in these HHS patients and 45% in HHS patients whose baseline HDL was below the median (46.4 mg/dL). Incidence of serious coronary events was similar for LOPID and placebo subgroups with baseline HDL above the median (46.4 mg/dL).[3]

Raised HDL levels 1½ to 3 times more effectively than lovastatin

—in a 12-week, double-blind, randomized trial among patients with moderate to severe hyperlipidemia. Lovastatin achieved greater reductions in total serum cholesterol than gemfibrozil in this study population.[4]

RAISES HDL
DRAMATICALLY REDUCES HEART ATTACK

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*Defined as a combination of definite coronary death and/or definite myocardial infarction.

References: 1. Goldstein JL, Hazzard WR, Schrott HG, Bierman EL, Motulsky AG. Hyperlipidemia in coronary heart disease. I. Lipid levels in 500 survivors of myocardial infarction. *J Clin Invest.* 1973;52:1533-1543. **2.** Assmann G, Schulte H. *PROCAM-Trial: Prospective Cardiovascular Münster Trial.* Zürich: Panscientia Verlag; 1986:8-9. **3.** Data on file, Medical Affairs Dept, Parke-Davis **4.** Tikkanen MJ, Helve E, Jäättelä A, et al. Comparison between lovastatin and gemfibrozil in the treatment of primary hypercholesterolemia: the Finnish Multicenter Study. *Am J Cardiol.* 1988;62:35J-43J.

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Lopid® (Gemfibrozil Capsules and Tablets)

Before prescribing, please see full prescribing information.
A Brief Summary follows.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease (See WARNINGS).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

During the Helsinki Heart Study and in the 1½ year follow-up period since the trial was completed, mortality from any cause was 59 (2.9%) in the Lopid group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the Lopid group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statistically-significantly different from the 29% excess mortality seen in the clofibrate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58% greater trend in the Lopid group (43 vs 27 patients in the placebo group, p=0.056).

In the Helsinki Heart Study, the incidence of total malignancies discovered during the trial and in the 1½ years since the trial was completed was 39 in the Lopid group and 29 in the placebo group (difference not statistically significant). This includes 5 basal cell carcinomas in the Lopid group and none in the placebo group (p=0.06; historical data predicted an expected 4.7 cases in the placebo group). GI malignancies and deaths from malignancies were not statistically different between Lopid and placebo subgroups. Follow-up of the Helsinki Heart Study participants will provide further information on cause-specific mortality and cancer morbidity.

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants – Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts – Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS. 1. **Initial Therapy** – Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy** – Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions** – (A) **Lovastatin:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility** – Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p=0.1). In high dose female rats, there was a significant increase in the combined incidence of benign, and malignant liver neoplasms. In male and female mice, there were no statistically significant differences from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately three or ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category B** – Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to Lopid. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lopid is tumorigenic in male and female rats, the use of Lopid in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers** – Because of the potential for tumorigenicity shown for gemfibrozil in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes** – Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. **Liver Function** – Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Use in Children** – Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In the double-blind controlled phase of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group (placebo incidence in parentheses): gastrointestinal reactions, 34.2% (23.8%), dyspepsia, 19.6% (11.9%); abdominal pain, 9.8% (5.6%); acute appendicitis (histologically confirmed in most cases where data are available), 1.2% (0.6%); atrial fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant difference between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5%); fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%).

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study.

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of **musculoskeletal symptoms** (See WARNINGS), and to **abnormal liver function tests** and **hematologic changes** (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patients.

Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *Integumentary:* alopecia.

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

MANAGEMENT OF OVERDOSE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

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STOP LESIONS FROM SURFACING

An alarming rise in the incidence of genital herpes points to the need for better disease treatment. Fortunately, long-term maintenance therapy with ZOVIRAX® can help keep herpes patients lesion-free. In controlled studies of 4 to 6 months' duration, recurrences were totally prevented in up to 75% of patients. And during two years of clinical use, daily therapy has been shown to be generally well tolerated.[1] One capsule TID...the best way to stop lesions from surfacing.

Reference. 1. Data on file, Burroughs Wellcome Co

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Brief Summary

INDICATIONS AND USAGE: Zovirax Capsules are indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes in certain patients.

The severity of disease is variable depending upon the immune status of the patient, the frequency and duration of episodes, and the degree of cutaneous or systemic involvement. These factors should determine patient management, which may include symptomatic support and counseling only, or the institution of specific therapy. The physical, emotional and psycho-social difficulties posed by herpes infections as well as the degree of debilitation, particularly in immunocompromised patients, are unique for each patient, and the physician should determine therapeutic alternatives based on his or her understanding of the individual patient's needs. Thus Zovirax Capsules are not appropriate in treating all genital herpes infections. The following guidelines may be useful in weighing the benefit/risk consideration in specific disease categories:

First Episodes (primary and nonprimary infections—commonly known as initial genital herpes):

Double-blind, placebo-controlled studies have demonstrated that orally administered Zovirax significantly reduced the duration of acute infection (detection of virus in lesions by tissue culture) and lesion healing. The duration of pain and new lesion formation was decreased in some patient groups. The promptness of initiation of therapy and/or the patient's prior exposure to Herpes simplex virus may influence the degree of benefit from therapy. Patients with mild disease may derive less benefit than those with more severe episodes. In patients with extremely severe episodes, in which prostration, central nervous system involvement, urinary retention or inability to take oral medication require hospitalization and more aggressive management, therapy may be best initiated with intravenous Zovirax.

Recurrent Episodes:

Double-blind, placebo-controlled studies in patients with frequent recurrences (6 or more episodes per year) have shown that Zovirax Capsules given for 4 to 6 months prevented or reduced the frequency and/or severity of recurrences in greater than 95% of patients. Clinical recurrences were prevented in 40 to 75% of patients. Some patients experienced increased severity of the first episode following cessation of therapy; the severity of subsequent episodes and the effect on the natural history of the disease are still under study.

The safety and efficacy of orally administered acyclovir in the suppression of frequent episodes of genital herpes have been established only for up to 6 months. Chronic suppressive therapy is most appropriate when, in the judgement of the physician, the benefits of such a regimen outweigh known or potential adverse effects. In general, Zovirax Capsules should not be used for the suppression of recurrent disease in mildly affected patients. Unanswered questions concerning the human relevance of *in vitro* mutagenicity studies and reproductive toxicity studies in animals given very high doses of acyclovir for short periods (see Carcinogenesis, Mutagenesis, Impairment of Fertility) should be borne in mind when designing long-term management for individual patients. Discussion of these issues with patients will provide them the opportunity to weigh the potential for toxicity against the severity of their disease. Thus, this regimen should be considered only for appropriate patients and only for six months until the results of ongoing studies allow a more precise evaluation of the benefit/risk assessment of prolonged therapy.

Limited studies have shown that there are certain patients for whom intermittent short-term treatment of recurrent episodes is effective. This approach may be more appropriate than a suppressive regimen in patients with infrequent recurrences.

Immunocompromised patients with recurrent herpes infections can be treated with either intermittent or chronic suppressive therapy. Clinically significant resistance, although rare, is more likely to be seen with prolonged or repeated therapy in severely immunocompromised patients with active lesions.

CONTRAINDICATIONS: Zovirax Capsules are contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulation.

WARNINGS: Zovirax Capsules are intended for oral ingestion only.

PRECAUTIONS: General: Zovirax has caused decreased spermatogenesis at high doses in some animals and mutagenesis in some acute studies at high concentrations of drug (see PRECAUTIONS—Carcinogenesis, Mutagenesis, Impairment of Fertility). The recommended dosage and length of treatment should not be exceeded (see DOSAGE AND ADMINISTRATION).

Exposure of Herpes simplex isolates to acyclovir *in vitro* can lead to the emergence of less sensitive viruses. The possibility of the appearance of less sensitive viruses in man must be borne in mind when treating patients. The relationship between the *in vitro* sensitivity of Herpes simplex virus to acyclovir and clinical response to therapy has yet to be established (see CLINICAL PHARMACOLOGY—Microbiology).

Because of the possibility that less sensitive virus may be selected in patients who are receiving acyclovir, all patients should be advised to take particular care to avoid potential transmission of virus if active lesions are present while they are on therapy. In severely immunocompromised patients, the physician should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses which may not fully respond to continued acyclovir therapy.

Drug Interactions: Co-administration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of 50, 150 and 450 mg/kg given by gavage. There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors. In 2 *in vitro* cell transformation assays, used to provide preliminary assessment of potential oncogenicity in advance of these more definitive life-time bioassays in rodents, conflicting results were obtained. Acyclovir was positive at the highest dose used in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice. Acyclovir was negative in another transformation system considered less sensitive.

In acute studies, there was an increase, not statistically significant, in the incidence of chromosomal damage at maximum tolerated parenteral doses of 100 mg/kg acyclovir in rats but not Chinese hamsters; higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters. In addition, no activity was found after 5 days dosing in a dominant lethal study in mice. In 6 of 11 microbial and mammalian cell assays, no evidence of mutagenicity was observed. At 3 loci in a Chinese hamster ovary cell line, the results were inconclusive. In 2 mammalian cell assays (human lymphocytes and L5178Y mouse lymphoma cells *in vitro*), positive responses for mutagenicity and chromosomal damage occurred, but only at concentrations at least 400 times the acyclovir plasma levels achieved in man.

Acyclovir has not been shown to impair fertility or reproduction in mice (450 mg/kg/day, p.o.) or in rats (25 mg/kg/day, s.c.). At 50 mg/kg/day s.c. in the rat, there was a statistically significant increase in post-implantation loss, but no concomitant decrease in litter size. In female rabbits treated subcutaneously with acyclovir subsequent to mating, there was a statistically significant decrease in implantation efficacy but no concomitant decrease in litter size at a dose of 50 mg/kg/day. No effect upon implantation efficiency was observed when the same dose was administered intravenously. In a rat peri- and postnatal study at 50 mg/kg/day s.c., there was a statistically significant decrease in the group mean numbers of corpora lutea, total implantation sites and live fetuses in the F_1 generation. Although not statistically significant, there was also a dose related decrease in group mean numbers of live fetuses and implantation sites at 12.5 mg/kg/day and 25 mg/kg/day, s.c. The intravenous administration of 100 mg/kg/day, a dose known to cause obstructive nephropathy in rabbits, caused a significant increase in fetal resorptions and a corresponding decrease in litter size. However, at a maximum tolerated intravenous dose of 50 mg/kg/day in rabbits, there were no drug-related reproductive effects.

Intraperitoneal doses of 320 or 80 mg/kg/day acyclovir given to rats for 1 and 6 months, respectively, caused testicular atrophy. Testicular atrophy was persistent through the 4-week postdose recovery phase after 320 mg/kg/day; some evidence of recovery of sperm production was evident 30 days postdose. Intravenous doses of 100 and 200 mg/kg/day acyclovir given to dogs for 31 days caused aspermatogenesis. Testicles were normal in dogs given 50 mg/kg/day i.v. for one month.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p.o.), rabbit (50 mg/kg/day, s.c. and i.v.) or in standard tests in the rat (50 mg/kg/day, s.c.). In a non-standard test in rats, fetal abnormalities, such as head and tail anomalies, were observed following subcutaneous administration of acyclovir at very high doses associated with toxicity to the maternal rat. The clinical relevance of these findings is uncertain. There are no adequate and well-controlled studies in pregnant women. Acyclovir should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Although acyclovir was not teratogenic in standard animal studies, the drug's potential for causing chromosome breaks at high concentration should be taken into consideration in making this determination.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Zovirax is administered to a nursing woman. In nursing mothers, consideration should be given to not using acyclovir treatment or discontinuing breastfeeding.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS—Short-Term Administration: The most frequent adverse reactions reported during clinical trials of treatment with Zovirax Capsules were nausea and/or vomiting in 8 of 298 patient treatments (2.7%) and headache in 2 of 298 (0.6%). Less frequent adverse reactions, each of which occurred in 1 of 298 patient treatments with Zovirax Capsules (0.3%), included diarrhea, dizziness, anorexia, fatigue, edema, skin rash, leg pain, inguinal adenopathy, medication taste and sore throat.

Long-Term Administration: The most frequent adverse reactions reported in studies of daily therapy for 3 to 6 months were headache in 33 of 251 patients (13.1%), diarrhea in 22 of 251 (8.8%), nausea and/or vomiting in 20 of 251 (8.0%), vertigo in 9 of 251 (3.6%), and arthralgia in 9 of 251 (3.6%). Less frequent adverse reactions, each of which occurred in less than 3% of the 251 patients (see number of patients in parentheses), included skin rash (7), insomnia (4), fatigue (7), fever (4), palpitations (1), sore throat (2), superficial thrombophlebitis (1), muscle cramps (2), pars planitis (1), menstrual abnormality (4), acne (3), lymphadenopathy (2), irritability (1), accelerated hair loss (1), and depression (1).

DOSAGE AND ADMINISTRATION: Treatment of initial genital herpes: One 200 mg capsule every 4 hours, while awake, for a total of 5 capsules daily for 10 days (total 50 capsules).

Chronic suppressive therapy for recurrent disease: One 200 mg capsule 3 times daily for up to 6 months. Some patients may require more drug, up to one 200 mg capsule 5 times daily for up to 6 months.

Intermittent Therapy: One 200 mg capsule every 4 hours, while awake, for a total of 5 capsules daily for 5 days (total 25 capsules). Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence.

Patients With Acute or Chronic Renal Impairment: One 200 mg capsule every 12 hours is recommended for patients with creatinine clearance ≤10 ml/min/1.73 m^2.

HOW SUPPLIED: Zovirax Capsules (blue, opaque) containing 200 mg acyclovir and printed with "Wellcome ZOVIRAX 200"—Bottles of 100 (NDC-0081-0991-55), and unit dose pack of 100 (NDC-0081-0991-56).

Store at 15°-30°C (59°-86°F) and protect from light and moisture.

U.S. Patent No. 4199574

*In controlled studies, recurrences were totally prevented for 4 to 6 months in up to 75% of patients.

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Continuing Medical Education

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

March 23-24—**Ophthalmic Reviews.** Mayo Clinic-Scottsdale at Scottsdale Sheraton Resort. Fri-Sat. Contact: Mayo Clinic-Scottsdale.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Jodi Lee Smith, Postgraduate Courses, Mayo Clinic Scottsdale, (602) 391-8300.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

March 27-30—**15th Annual Primary Care Update.** Arizona Health Sciences Center, Tucson. Tues-Fri. Contact: Lynne Mascarella, (602) 626-7832.

March 29-30—**Clinical Reviews.** Mayo Clinic-Scottsdale at The Registry Resort, Scottsdale. Thurs-Fri. Contact: Mayo Clinic-Scottsdale.

March 31—**Nutrition Update for Primary Care Providers.** Arizona Health Sciences Center, Tucson. Sat. Contact: Lynne Mascarella, (602) 626-7832.

March 31—**Primary Management of Common Cardiovascular Conditions.** Mayo Clinic-Scottsdale at The Registry Resort, Scottsdale. Sat. Contact: Mayo Clinic-Scottsdale.

April 9-14—**Primary Care Update.** Tucson. Mon-Sat. Contact: Cristy Snow, (602) 626-7946.

April 20-21—**Series I—Coronary Heart Disease Update.** Medical Education Resources at La Posada Resort, Scottsdale. Fri-Sat. Contact: Deborah Helton, 1 (800) 421-3756.

April 21—**26th Annual Arizona Chest Symposium.** Tucson Medical Center, Tucson. Sat. Contact: Susan Thornton, (602) 324-1879.

May 4—**Infectious Diseases Update: 1990.** Mayo Clinic-Scottsdale. Fri. Contact: Shelia Collins, (602) 391-8300.

May 14-18—**22nd Annual Southwestern School for Behavioral Health Studies.** University of Arizona, Tucson. Mon-Fri. Contact: Susan Villaescusa, (602) 721-3838.

June 22-24—**Thirteenth Annual Pediatrics in the Red Rocks.** American Academy of Pediatrics—Arizona Chapter at Los Abrigados, Sedona. Fri-Sun. Contact: Melanye Wrighton, (602) 230-1949.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

March 17-18—**35th Postgraduate Assembly of Los Angeles County Society of Anesthesiologists.** Los Angeles County Society of Anesthesiologists at Sheraton Universal Hotel, Universal City. Sat-Sun. Contact: LACSA, PO Box 3465, Los Angeles 90051-1465. (213) 483-1581, ext 320.

March 24-25—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Newport Beach Marriott Hotel. Sat-Sun. 9 hrs. $125. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

May 17-20—**California Society of Anesthesiologists 1990 Annual Meeting.** California Society of Anesthesiologists at San Francisco Marriott. Thurs-Sun. 18 hrs. $175. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

May 29-June 3—**UCSD Anesthesiology Review Course.** UCSD at San Diego Princess, San Diego. Tues-Sun. Contact: UCSD.

CARDIOLOGY

March 30-31—**Cardiology for the Clinician.** UCI at Long Beach. Fri-Sat. Contact: UCI.

April 2-11—**Cardiology for the Consultant: A Physicians' Retreat.** Scripps Clinic and Research Foundation at Rancho Santa Fe. 1½ weeks. 40 hrs. $900. Contact: Mary Ann Morris, 860 SW Scherer Rd, Lee's Summit, MO 64063. (816) 524-5780.

April 28—**Current Concepts in Heart Disease.** Grossmont Hospital at Bahia Hotel, San Diego. Sat. 6 hrs. $100. Contact: Continuing Medical Education, Grossmont Hospital, PO Box 158, La Mesa 92044. (619) 589-4153.

May 4-5—**Series II—Arrhythmias: Interpretation, Diagnosis, and Management.** Medical Education Resources at Marriott Hotel, San Diego. Fri-Sat. Contact: MER, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4528. (303) 798-9682.

May 5-6—**The Cardiac Patient: Current Controversies and Clinical Decision Making.** Saddleback Memorial Medical Center's Heart Institute at Four Seasons Hotel, Newport Beach. Sat-Sun. $150. Contact: Saddleback Memorial Education Department, (714) 837-4500, ext 3639.

June 15-16—**Series IV—Cardiac Wellness and Rehabilitation.** Medical Education Resources at Hyatt Union Square, San Francisco. Fri-Sat. Contact: MER, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4528. (303) 798-9682.

June 22-23—**Series I—Coronary Heart Disease Update.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sat. Contact: MER, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4528. (303) 798-9682.

August 3-4—**Series II—Arrhythmias: Interpretation, Diagnosis, and Management.** Medical Education Resources at Anaheim. Fri-Sat. Contact: MER, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

August 17-18—**Series IV—Cardiac Wellness and Rehabilitation.** Medical Education Resources at Monterey. Fri-Sat. Contact: MER, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

(Continued on Page 238)

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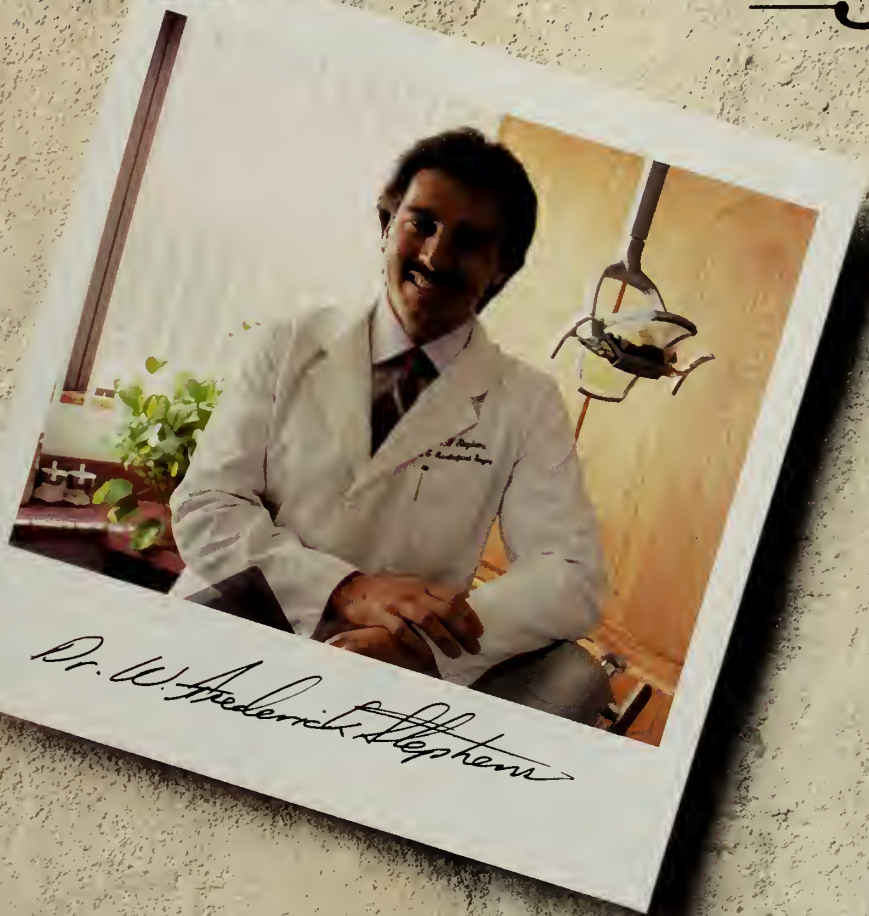

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CONTINUING MEDICAL EDUCATION

(Continued from Page 236)

DERMATOLOGY

June 8-9—**Southwestern Regional Cutaneous Flap Workshop.** UCLA. Fri-Sat. 15 hrs. Contact: Daniel E. Gormley, 412 W Carroll, Ste 207, Glendora 91740. (818) 963-7684.

August 3-4—**Southwestern Regional Cryostat and Microscopically Controlled Surgical Workshop.** UCSD. 15 hrs. Contact: Daniel E. Gormley, MD, 412 W Carroll, Ste 207, Glendora 91740. (818) 963-7684.

August 16-19—**Advanced Seminars in Dermatology.** UCSD at Catamaran Resort Hotel, San Diego. Thurs-Sun. Contact: UCSD.

EMERGENCY MEDICINE

March 19-23—**Emergency Medicine Symposium II.** UCSD at La Jolla Marriott Hotel. Mon-Fri. 32 hrs. Contact: UCSD.

March 21-23—**Advances in Emergency Medicine 1990.** UCSF at Mark Hopkins Hotel, San Francisco. Wed-Fri. 22 hrs. $425. Contact: UCSF.

April 7-14—**Cardiopulmonary Emergencies.** American Postgraduate Institute of Postgraduate Education and Scripps Memorial Hospital Encinitas at Poipu Beach Hotel & Waiohai Resort, Kauai, Hawaii. One week. Contact: Edith S. Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

April 19-22—**9th Annual Emergency Medicine and Acute Care: A Critical Appraisal, Series 3.** Emergency Medical Abstracts at San Francisco. Thurs-Sun. 20 hrs. Contact: Robert Cowsill, 6917 Royer Ave, West Hills 91307. (818) 884-8844.

May 7-11—**Emergency Medicine Symposium I: Cardiology, Pulmonary, Neurology.** UCSD at San Diego Hilton Beach and Tennis Resort. Mon-Fri. 32 hrs. $450. Contact: UCSD.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Avenue, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7186.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

May 16-20—**12th Annual: Wound Management Workshop.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sun. 19 hrs. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

May 27-31—**Annual Scientific Assembly.** California Chapter of the American College of Emergency Physicians at Silverado Country Club, Napa. Sun-Thurs. 18 hrs. CAL/ACEP, (213) 374-4039.

June 25-29—**Emergency Medicine Symposium III: Pediatrics.** UCSD at San Diego Hilton Beach and Tennis Resort. Mon-Fri. 32 hrs. $450. Contact: UCSD.

August 1-5—**Wilderness Medicine: '90.** American College of Emergency Physicians at Squaw Valley Lake Tahoe, Nevada. Wed-Sun. 22 hrs. $395. Contact: Eugene Allred, MD, PO Box 321, Yreka 96097. (800) 888-5632.

August 20-24—**Emergency Medicine Symposium II: Trauma and Surgery.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $450. Contact: UCSD.

FAMILY PRACTICE/PRIMARY CARE

March 28-30—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF at Hyatt Regency Hotel, San Francisco. Wed-Fri. 16 hrs. Contact: UCSF.

March 31-April 7—**Primary Care Medicine.** UCSF at Maui Marriott, Hawaii. One week. 20 hrs. $475. UCSF.

April 18-20—**40th Annual Course for Physicians in Family Practice: Practice in the 1990s.** Wed-Sat. Contact: Mary P. Arnold, Mount Zion Hospital and Medical Center, PO Box 7921, San Francisco 94120. (415) 885-7270.

June 3-8—**14th Annual Fingers to the Toes: Primary Care Orthopaedics.** UCD at Stanford Sierra Camp, Fallen Leaf Lake. Sun-Fri. Contact: UCD.

June 11-15—**UCI Family Practice Refresher Course.** Memorial/UCI Center for Health Education at Westin South Coast Plaza, Costa Mesa. Mon-Fri. 29 hrs. Contact: UCI.

July 9-12—**Family Practice Board Review Course.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Thurs. 25 hrs. Contact: UCSF.

INTERNAL MEDICINE

March 15-17—**5th International Conference on Monoclonal Antibody Immunoconjugates for Cancer.** UCSD at Sheraton Harbor Island East, San Diego. Thurs-Sat. Contact: UCSD.

March 24-29—**American Society of Clinical Pathologists and College of American Pathologists: 1990 Spring Meeting** at San Francisco Civic Auditorium. Sat-Thurs. Contact: ASCP/CAP National Meeting, PO Box 12075, Chicago, IL 60612-0075. (800) 621-4142.

April 18-20—**Advances in Infectious Diseases.** UCSD at Fairmont Hotel, San Francisco. Wed-Fri. 18 hrs. $380. Contact: UCSF.

April 21—**5th Annual Conference: New Treatments in Chronic Liver Disease.** Scripps Clinic and Research Foundation at Amphitheater of the Green Hospital, Scripps Clinic, La Jolla. Sat. $125. Contact: Bonny Mower, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 14-18—**Hyperbaric Medicine.** UCI/Memorial Medical Center. 36 hrs. $650. Contact: Celia Loney, (213) 595-3613.

May 18-20—**8th Symposium on Frontiers of Rheumatology.** Annenberg Center for Health Sciences. Fri-Sun. Contact: ACHS, 39000 Bob Hope Dr, Rancho Mirage 92270. (800) 321-3690.

June 4-5—**TMJ Arthroscopy: Rationale, Treatment, and Management.** UCSD. Mon-Tues. Contact: UCSD.

June 11-15—**Advances in Internal Medicine.** UCSF at San Francisco Marriott Hotel. Mon-Fri. 33 hrs. $535. Contact: UCSF.

June 26-30—**Advances in Internal Medicine.** UCSF at Cole Hall, San Francisco. Tues-Sat. 33 hrs. $535. Contact: UCSF.

OB/GYN

March 21-23—**Advanced Fetal Heart Rate Monitoring.** UCI at Newport Marriott Hotel, Newport Beach. Wed-Fri. Contact: UCI.

March 22-24—**Geriatric Gynecology With Special Emphasis on Urinary Incontinence.** UCI at Palm Springs. Thurs-Sat. Contact: UCI.

(Continued on Page 242)

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Investigators' evaluations confirm hair growth in male pattern baldness of the vertex

ROGAINE® Topical Solution (minoxidil 2%) is the *first* prescription medication proved effective for male pattern baldness of the vertex. The effect on frontal baldness has not been adequately studied.

Evidence of growth was demonstrated by physician evaluations of 1,431 patients in 27 centers across the United States. Patients were placed on ROGAINE or placebo and evaluated each month for four months. Response was judged to be no growth, new vellus (baby) hair, or minimal, moderate, or dense growth.

In addition, after the placebo group was discontinued, continuous application of ROGAINE over an additional eight months was evaluated to determine if nonvellus growth could be sustained.

START OF STUDY

START OF STUDY

START OF STUDY

Examples of minimal, moderate, and dense growth as evaluated by investigators

© 1989 The Upjohn Company

MINIMAL GROWTH

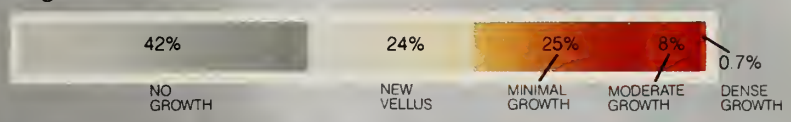
MODERATE GROWTH

DENSE GROWTH

Four-Month Phase

At the end of four months, 34% of 714 patients treated with ROGAINE were evaluated as showing minimal, moderate, or dense growth, while 20% of 717 patients showed minimal, moderate, or dense growth with placebo, a highly significant difference ($P<.0005$).

Rogaine (714)

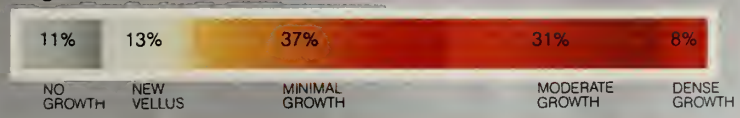


Placebo (717)

Non-Placebo-Controlled Continuation Phase

After 12 months, dense growth was observed in 8% of the 619 patients treated with ROGAINE, moderate growth in 31%, and minimal growth in 37%. Approximately one fourth of patients showed only vellus hair growth or no growth.

Rogaine (619)



Compliance is Essential

The multicenter studies indicate that a period of *four months or longer* of daily b.i.d. applications of ROGAINE is usually necessary before evidence of hair growth is apparent. Hair growth continued to increase in study subjects over months 5 through 12.

Continuous use is necessary to maintain hair growth. Newly grown hair returns to the untreated state three to four months after cessation of therapy with ROGAINE.

Please see last page for brief summary of prescribing information.

Rogaine® Rx

TOPICAL SOLUTION minoxidil 2%

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Rogaine® Rx

TOPICAL SOLUTION minoxidil 2%®

INDICATIONS AND USAGE
Male pattern baldness (alopecia androgenetica) of the vertex of the scalp. No effect has been seen on frontal baldness. At least four months of treatment are generally required before evidence of hair growth can be expected, further growth continues through one year. The new growth is not permanent; cessation of treatment will lead to its loss in a few months.

CONTRAINDICATIONS
Hypersensitivity to minoxidil, propylene glycol or ethanol.

WARNINGS
1. Need for normal scalp. Before starting treatment, make sure that the patient has a normal, healthy scalp. Local abrasion or dermatitis may increase absorption and hence the risk of side effects.
2. Potential adverse effects. Although extensive use of topical minoxidil has not revealed evidence that enough minoxidil is absorbed to have systemic effects, greater absorption due to misuse, individual variability or unusual sensitivity could, at least theoretically, produce a systemic effect.
Experience with oral minoxidil has shown the following major cardiovascular effects (Review the package insert for LONITEN® Tablets for details):
—salt and water retention, generalized and local edema
—pericardial effusion, pericarditis, tamponade
—tachycardia
—increased incidence of angina or new onset of angina
Patients with underlying heart disease, including coronary artery disease and congestive heart failure, would be at particular risk of these potential effects. Additive effects could also emerge in patients being treated for hypertension.
Potential patients should have a history and physical, should be advised of potential risks and a risk/benefit decision should be made. Heart patients should realize that adverse effects may be especially serious. Alert patients to the possibility of tachycardia and fluid retention, and monitor for increased heart rate, weight gain or other systemic effects.

PRECAUTIONS
General Precautions. Monitor patients one month after starting ROGAINE and at least every six months afterward. Discontinue ROGAINE if systemic effects occur. The alcohol base will burn and irritate the eye. If ROGAINE reaches sensitive surfaces (eg, eye, abraded skin and mucous membranes) bathe with copious cool water.
Avoid inhaling the spray.
Do not use in conjunction with other topical agents such as corticosteroids, retinoids and petrolatum or agents that enhance percutaneous absorption. ROGAINE is for topical use only. Each mL contains 20 mg minoxidil and accidental ingestion could cause adverse systemic effects.
Decreased integrity of the epidermal barrier caused by inflammation or disease of the skin, eg, excoriations, psoriasis or severe sunburn, may increase minoxidil absorption.
Patient Information: A patient information leaflet is included with each package and in the full product information.
Drug Interactions. No drug interactions are known. Theoretically, absorbed minoxidil may potentiate orthostatic hypotension in patients taking guanethidine.
Carcinogenesis, Mutagenesis and Impairment of Fertility: No carcinogenicity was found with topical application. Oral administration may be associated with an increased incidence of malignant lymphomas in female mice and hepatic nodules in male mice. In rats, there was a dose-dependent reduction in conception rate.
Pregnancy Category C. ROGAINE should not be used by pregnant women.
Labor and Delivery. The effects are not known.
Nursing Mothers. ROGAINE should not be administered.
Pediatric Use. Safety and effectiveness have not been established under age 18.

ADVERSE REACTIONS
ROGAINE was used by 3510 patients in placebo-controlled trials. Except for dermatologic events, no individual reaction or reactions grouped by body systems appeared to be increased in the minoxidil-treated patients.
Respiratory (bronchitis, upper respiratory infection, sinusitis) 5.95%, **Dermatologic** (irritant or allergic contact dermatitis) 5.27%, **Gastrointestinal** (diarrhea, nausea, vomiting) 3.42%, **Neurology** (headache, dizziness, faintness, light-headedness) 2.56%, **Musculoskeletal** (fractures, back pain, tendinitis) 2.17%, **Cardiovascular** (edema, chest pain, blood pressure increases/decreases, palpitation, pulse rate increases/decreases) 1.28%, **Allergy** (non-specific allergic reactions, hives, allergic rhinitis, facial swelling and sensitivity) 1.03%, **Special Senses** (conjunctivitis, ear infections, vertigo) 0.94%, **Metabolic-Nutritional** (edema, weight gain) 0.60%, **Urinary Tract** (urinary tract infections, renal calculi, urethritis) 0.46%, **Genital Tract** (prostatitis, epididymitis) 0.46%, **Psychiatric** (anxiety, depression, fatigue) 0.28%, **Hematology** (lymphadenopathy, thrombocytopenia) 0.23%, **Endocrine** 0.09%.
Patients have been followed for up to 5 years and there has been no change in incidence or severity of reported reactions. Additional events reported since marketing include: eczema, hypertrichosis, local erythema, pruritus, dry skin/scalp flaking, sexual dysfunction, visual disturbances including decreased visual acuity, exacerbation of hair loss, alopecia.

DOSAGE AND ADMINISTRATION
Hair and scalp should be dry before application. 1 mL should be applied to the total affected areas twice daily. Total daily dose should not exceed 2 mL. If the fingertips are used to facilitate drug application, wash the hands afterwards.

HOW SUPPLIED
60 mL bottle with multiple applicators NDC 0009-3367-05
Caution: Federal law prohibits dispensing without a prescription.

B-1-S

Upjohn
The Upjohn Company
Kalamazoo, MI 49001 USA

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CONTINUING MEDICAL EDUCATION

(Continued from Page 238)

April 19-20—**Prenatal Genetics Diagnosis and Fetal Therapy.** UCI at Red Lion Hotel, Costa Mesa. Thurs-Fri. Contact: UCI.

April 28—**Symposium on Gynecologic Oncology.** Scripps Clinic and Research Foundation at La Jolla. Sat. 7 hrs. Contact: Bonny Mower, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

June 1-3—**Advanced Fetal Heart Rate Monitoring.** UCI at Monterey Plaza Hotel. Fri-Sun. Contact: UCI.

August 17-19—**3rd Annual Perinatal Review.** Memorial/UCI Center for Health Education at Four Seasons Hotel, Newport Beach. Fri-Sun. Contact: UCI.

August 21-25—**8th Annual Controversies in OB/GYN.** Memorial/UCI Center for Health Education at Mauna Kea, Hawaii. Tues-Sat. Contact: UCI.

OCCUPATIONAL AND ENVIRONMENTAL MEDICINE

May 31-June 1—**Occupational and Environmental Medicine.** UCD at Capitol Plaza Holiday Inn, Sacramento. Fri-Sat. Contact: UCD.

OPHTHALMOLOGY

March 31—**Ocular Inflammation.** Scripps Clinic and Research Foundation at La Jolla. Sat. 8 hrs. $90. Contact: Susan Buntjer, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

PATHOLOGY

May 26—**Fine Needle Aspiration Tutorials.** UCSF. Sat. 7 hrs. $550. Contact: UCSF.

PEDIATRICS

March 30-31—**Neurodevelopmental Assessment of 4-9 Year Old Children.** Children's Hospital Oakland. Fri-Sat. 12 hrs. $150. Contact: Kim Leadon, Children's Hospital Oakland, 747 52nd St, Oakland 94609. (415) 428-3021.

April 6-7—**Annual Ambulatory Pediatrics.** UCD at Hilton Inn, Sacramento. Fri-Sat. 16 hrs. $175. Contact: UCD.

April 19-20—**9th Annual Child Abuse.** UCD at Radisson Hotel, Sacramento. Thurs-Fri. 12 hrs. $135. Contact: UCD.

May 17-19—**23rd Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. 16 hrs. $300. Contact: UCSF.

June 29-30—**Current Concepts in Pediatric Allergy and Otolaryngology.** Children's Hospital San Diego at Hyatt Islandia Hotel, San Diego. Fri-Sat. Contact: Continuing Medical Education Office, Children's Hospital, (619) 576-4072.

PREVENTIVE MEDICINE

June 3—**Therapeutic Frontiers.** UCLA at Miramar Sheraton Hotel, Santa Monica. Sun. 6 hrs. $50. Contact: UCLA.

PSYCHIATRY

March 16-19—**Advanced Medical Hypnosis.** UCSD at The Inn Rancho Santa Fe. Fri-Sun. Contact: UCSD.

April 23-27—**Introduction to Medical Hypnosis.** UCSD at The Inn at Del Mar. Mon-Fri. Contact: UCSD.

April 28-29—**The Cutting Edge 1990—The Heart of the Matter: Helping Improve Relationships.** UCSD at La Jolla Marriott Hotel. Fri-Sat. 13 hrs. $300. Contact: Cass Jones, 7916 Convoy Court, San Diego 92111. (619) 565-9921.

June 8-9—**The Threat to the Cosmic Order: Psychological, Social, and Health Implications of Richard Wagner's Ring of the Nibelung.** UCSF at Laurel Heights Campus, San Francisco. Fri-Sat. Contact: UCSF.

RADIOLOGY

March 16-18—**OB/GYN and Abdominal Sonography: Update 1989.** UCSF at Hyatt Regency, San Francisco. Fri-Sun. 15 hrs. $350. Contact: UCSF.

(Continued on Page 243)

CONTINUING MEDICAL EDUCATION

(Continued from Page 242)

March 19-23—**33rd Annual Postgraduate Course in Diagnostic Radiology.** UCSF at Fairmont Hotel, San Francisco. Mon-Fri. 32 hrs. $515. Contact: UCSF.

March 19-23—**American Society of Neuroradiology: 28th Annual Meeting.** American Society of Neuroradiology at Century Plaza Hotel and Tower, Los Angeles. Mon-Fri. Contact: ASNR, 1415 W 22nd St, Tower B, Oak Brook, IL 60521. (312) 574-8082.

March 26-30—**Diagnostic Imaging: 1990.** UCSF at Kauai, Hawaii. Mon-Fri. 23 hrs. $515. Contact: UCSF.

April 15-20—**10th Annual San Diego Residents Radiology Review Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 39 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 21—**Introduction to Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Sat. 8 hrs. $100. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

May 22-25—**CT and MRI in Body Imaging: A Comprehensive Course.** Tues-Fri. 15 hrs. $515. Contact: UCSF.

June 12-16—**Computer Assisted Radiology.** UCI at Anaheim Hilton Hotel. Tues-Sat. Contact: UCI.

July 22-26—**Napa Valley Imaging Update: MRI 1990.** UCD at Silverado Country Club, Napa. Sun-Thurs. 17 hrs. $445. Contact: UCD.

July 23-25—**Musculoskeletal Imaging.** Hoag Memorial Hospital, Department of Radiology at Ritz-Carlton Resort Hotel, Laguna Niguel. Mon-Wed. 15 hrs. $350. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 26-29—**4th Annual Symposium on Magnetic Resonance Imaging.** Hoag Memorial Hospital, Department of Radiology at Ritz-Carlton Resort Hotel, Laguna Niguel. Thurs-Sun. 22 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

August 23-28—**6th Annual Physics and Biology of Radiology.** UCSD at Hanalei Hotel, San Diego. Thurs-Tues. 25 hrs. $395. Contact: UCSD.

SURGERY

March 1990-December 1990—**Temporal Bone Surgical Dissection Courses: 1989.** House Ear Institute, 5 days per month. 53 hrs. $975. Contact: Antonio De la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

March 1990-June 1990—**Microsurgery Training Courses.** UCSD at Grossmont Hospital, La Mesa. 40 hrs. $1125. Contact: UCSD.

March 15-18—**10th Annual San Diego Cardiothoracic Surgery Symposium: Pathophysiology and Techniques of Cardiopulmonary Bypass.** Cardiothoracic Research and Education Foundation at San Diego Marriott Hotel and Marina. Thurs-Sun. 17 hrs. $300. Contact: CREF, PO Box 33185, San Diego 92103. (619) 692-9115.

March 15-18—**Surgical Forum.** Society of Graduate Surgeons of Los Angeles County and USC Medical Center at Beverly Hilton, Beverly Hills. Thurs-Sun. Contact: Director, Society of Graduate Surgeons, 5820 Wilshire Blvd, Ste 500, Los Angeles 90036. (213) 937-5514.

March 23-24—**Aesthetic Surgery of the Face.** UCSF at San Francisco. Fri-Sat. 13 hrs. $750. Contact: UCSF.

April 7-8—**Automated Percutaneous Discectomy Workshop.** UCSF. Sat-Sun. 12 hrs. $800. Contact: UCSF.

April 19-20—**General Thoracic Surgery.** American College of Chest Physicians at Tropicana Hotel, Las Vegas. Thurs-Fri. 13 hrs. $275. Contact: ACCP, 911 Busse Hwy, Park Ridge, IL 60068. (708) 698-2200.

May 19—**Prosthetics-Orthotics Course.** UCD at UCD Medical Center, Sacramento. Sat. Contact: UCD.

June 17-22—**Anatomic Basis for Aesthetic Surgery: Hands-On Laboratory Course.** UCD at Hyatt Regency, Sacramento. Sun-Fri. Contact: UCD.

June 21-23—**7th Annual San Diego Meeting on Arthroscopic Surgery of the Shoulder.** Tri-City Medical Center at La Jolla Marriott Hotel. Thurs-Sat. Contact: James C. Esch, MD, 3905 Waring Rd, Oceanside 92056. (619) 598-0080.

July 17-21—**6th Annual Superficial Anatomy and Cutaneous Surgery.** UCSD at La Jolla Marriott. Tues-Sat. Contact: UCSD.

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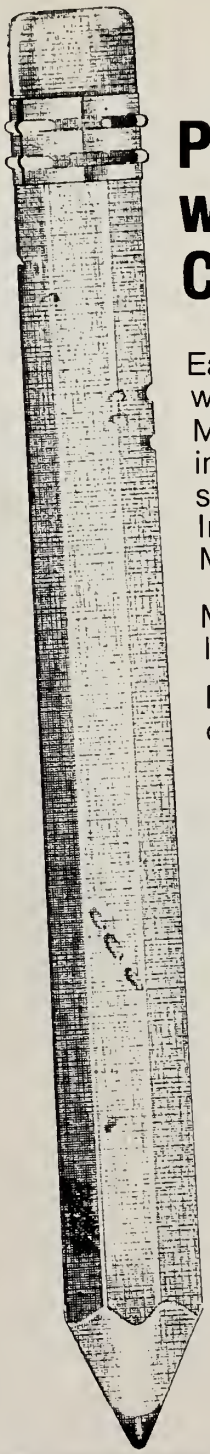

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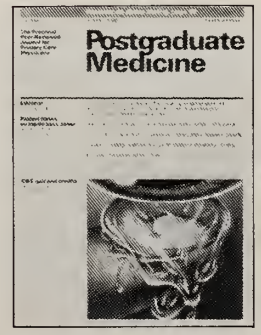

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(Continued from Page 243)

OF INTEREST TO ALL PHYSICIANS

March 13-18—**Wilderness Medicine: '90.** American College of Emergency Physicians at Squaw Valley, Lake Tahoe. Tues-Sun. 22 hrs. $395. Contact: Eugene Allred, PO Box 321, Yreka 96097. (916) 842-4667.

March 14—**Rationing Health Care.** Enloe Hospital at Esplanade Building, Chico. Wed. Contact: Linda Morgado, (916) 891-7300, ext. 7375.

March 19-22—**The Best Approach 1990: Effective, Efficient Strategies in Orthopaedics/Sports Medicine, Cardiology, Gynecology, and Infectious Disease.** Group Health Cooperative of Puget Sound at Intercontinental Hotel, Wailea, Maui, Hawaii. Mon-Thurs. 20 hrs. $325. Contact: GHCPS, CX-5, 201 16th Ave East, Seattle, WA 98112. (206) 326-6262.

March 24-25—**The Complaint of Insomnia in the Practice of Medicine: Scripps Clinic Sleep Update.** Scripps Clinic and Research Foundation. Sat-Sun. 11 hrs. $150. Contact: Susan Buntjer, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 29-31—**Facing the Challenge.** Scripps Memorial Hospital at Hyatt Regency, La Jolla. Thurs-Sat. 21 hrs. $300. Contact: Nomi Feldman, 5665 Oberlin Dr, Ste 110, San Diego 92121. (619) 453-6222.

April 27—**Alzheimer's Update.** UCD at Beverly Garland Hotel, Sacramento. Fri. Contact: UCD.

June 21-23—**Nevada State Medical Association Annual Meeting.** Nevada State Medical Association at Hyatt Lake Tahoe, Nevada. Thurs-Sat. Contact: Nevada State Medical Association, 3660 Baker Lane, Reno, NV 89509. (702) 825-6788.

July 9-13—**2nd Annual Marine Medicine.** UCSD at San Diego Princess. Mon-Fri. Contact: UCSD.

July 19-22—**Radiology for Non-Radiologists.** UCSD at Hotel del Coronado, San Diego. Thurs-Sun. 26 hrs. $295. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077. (404) 641-9773.

July 23-27—**4th Annual Sports Medicine.** UCSD at San Diego Princess. Mon-Fri. Contact: UCSD.

IDAHO

March 22-23—**Idaho Thoracic Society—Annual Medical Symposium.** Anderson Center, Boise. Thurs-Fri. Contact: Idaho Thoracic Society, PO Box 33, Boise 83707. (208) 344-6567.

May 9-12—**Snake River Medical Forum.** Lewiston. Wed-Sat. Contact: Nita Shoemaker, Program Coordinator, St Joseph Regional Medical Center, PO Box 816, Lewiston 83501. (208) 799-5416.

May 17-19—**Idaho Academy of Family Physicians—Annual Meeting.** Red Lion Riverside, Boise. Thurs-Sat. Contact: Mrs Irma Sparks, Exec Dir, Idaho Academy of Family Physicians, PO Box 175, Boise 83701. (208) 362-4808.

July 26-28—**Idaho Medical Association—Annual Meeting.** Sun Valley. Thurs-Sun. Contact: Idaho Medical Association, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

March 15-18—**Medicine in Transition—Apathy or Renewal?** Albuquerque. Contact: John R. Graham, MD, Albuquerque Centre for Psychotherapy, 7521 Lantern Rd, NE, Albuquerque 87109. (505) 883-6959.

March 17—**Illness Behavior.** Psychiatric Medical Association of New Mexico at University of New Mexico, Department of Nursing and Pharmacy, Albuquerque. Fri. Contact: Psychiatric Medical Assn, (505) 841-3511.

March 19-23—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Fri. Contact: American Educational Institute, (800) 354-3507.

March 26-30—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Fri. Contact: American Educational Institute, (800) 354-3507.

March 30-31—**Can OB/GYN Survive Liability?** Albuquerque Convention Center. Fri-Sat. Contact: Mary R. Boning, Office of Medical Education and Research, Presbyterian Hospital, (505) 841-1225.

April 2-6—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Fri. Contact: American Educational Institute, (800) 354-3507.

April 9-13—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Fri. Contact: American Educational Institute, (800) 354-3507.

May 4-5—**103rd Annual Meeting of the New Mexico Medical Society.** Albuquerque. Fri-Sat. Contact: Glenn Taylor, New Mexico Medical Society, 7770 Jefferson, NE, Albuquerque 87109. (505) 828-0237.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

March 30-31—**Current Progress in the Treatment of Arthritis** (Sponsor: UUMC). Fri-Sat. Prospector Square, Park City. Contact: (801) 581-8664.

April 7—**Sports Medicine Update** (Sponsor: UUMC). Sat. University of Utah, Salt Lake City. Contact: (801) 581-8664.

April 7-8—**Pulmonary Infectious Diseases** (Sponsor: UUMC). Sat-Sun. Stein Erickson Lodge, Park City. Contact: (801) 581-8664.

April 27-28—**Update in Disorders of the Esophagus** (Sponsor: UUMC). Fri-Sat. Marriott Hotel, Salt Lake City. Contact: (801) 581-8664.

May 3-4—**Ethics and Health** (Sponsor: UUMC). Thurs-Fri. University of Utah Health Science Center, Salt Lake City. Contact: (801) 581-8664.

(Continued on Page 246)

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CONTINUING MEDICAL EDUCATION

(Continued from Page 244)

May 11-12—**Update in Hyperlipidemias** (Sponsor: UUMC). Fri-Sat. Holiday Inn, St George. Contact: (801) 581-8664.

June 17-22—**School on Alcoholism and Other Drug Dependencies** (Sponsor: UUMC). Sun-Fri. University of Utah, Salt Lake City. Contact: (801) 538-3956.

July 8-14—**Update in Internal Medicine: Board Review Course** (Sponsor: UUMC). Sun-Sat. Cliff Lodge, Snowbird. Contact: (801) 581-8664.

October 4-5—**Ethics and Health** (Sponsor: UUMC). Thurs-Sat. University of Utah Alumni House, Salt Lake City. Contact: (801) 581-8664.

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

March 15-16—**Primary Care Orthopaedics.** Seattle. Thurs-Fri. Contact: U/W.

March 21—**Drugs.** Seattle. Wed. Contact: Northwest Hospital, (206) 364-0500.

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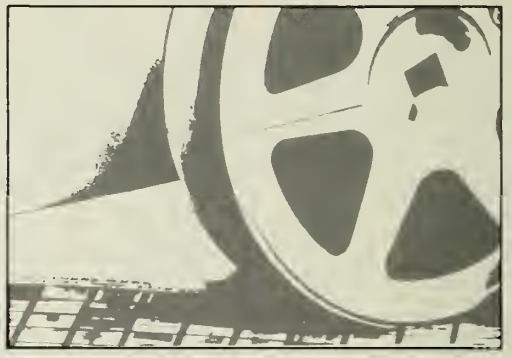

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CONTINUING MEDICAL EDUCATION

(Continued from Page 246)

March 21-23—**Recent Advances in Cancer Detection.** Seattle. Wed-Fri. Contact: U/W.

March 26-April 6—**Physical Medicine and Rehabilitation.** Bellevue. Mon-Sun. Contact: U/W.

March 29-31—**Trauma and the Elderly.** Seattle. Thurs-Sat. Contact: U/W.

April 6—**A Day of Infectious Disease.** Seattle. Fri. Contact: VMMC.

April 12—**Psychopharmacology.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

April 13-14—**Tacoma Surgical Club.** Tacoma. Fri-Sat. Contact: (206) 627-7137.

April 13-14—**Sixth Annual Benton-Franklin County Medical Society Medical Seminar.** Tri-Cities. Fri-Sat. Contact: (509) 783-8616.

April 27—**Dermatology.** Tacoma. Fri. Contact: (206) 627-7137.

May 4-5—**Orthopedic Review.** Seattle. Fri-Sat. Contact: VMMC.

May 10—**Nutrition.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

May 10-11—**Aggressive Musculoskeletal and Spinal Evaluation, Treatment, and Rehabilitation.** Tacoma. Thurs-Fri. Contact: CME Pierce County.

May 18-19—**Applications of Doppler Ultrasound.** Seattle. Fri-Sat. Contact: VMMC.

June 8-9—**Common Anorectal Disorders: A Medical and Surgical Approach.** Seattle. Fri-Sat. Contact: VMMC.

June 14-15—**Orthopaedics.** Seattle. Thurs-Fri. Contact: Northwest Hospital, (206) 364-0500.

June 16—**AIDS Issues 1990.** Kirkland. Sat. Contact: Evergreen Hospital, (206) 823-7599.

June 25-26—**Advanced Cardiac Life Support.** Tacoma. Mon-Tues. Contact: CME Pierce County.

September 20—**Orthopedics.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

October 11—**Diabetes.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

November 8—**Pediatrics.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

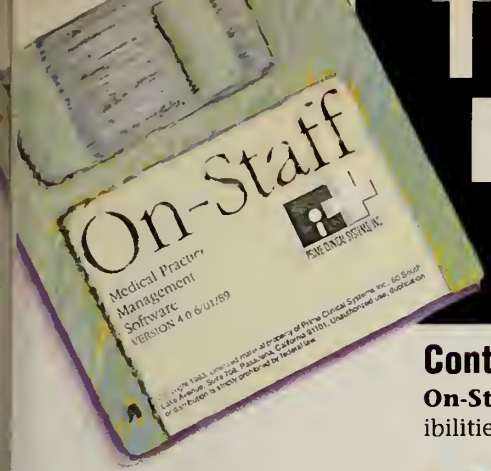
WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WYOMING

June 14-16—**Wyoming Medical Society—Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sat. Contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424.

August 8-11—**American College of Surgeons, Montana—Wyoming Chapter.** Jackson Hole. Wed-Sat. Contact: Robert C. Ratcliff, MD, 940 E Third St, Casper 82601. (307) 577-4223. ◆



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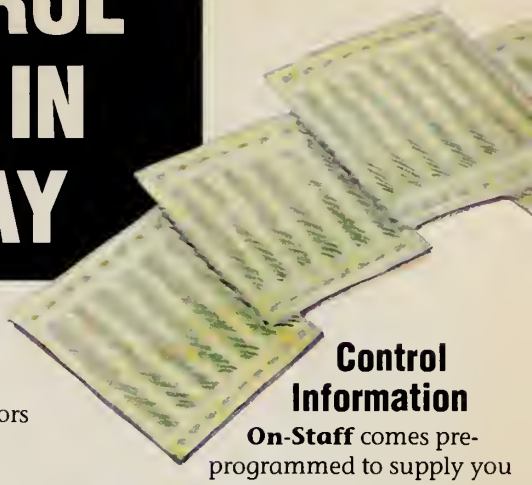

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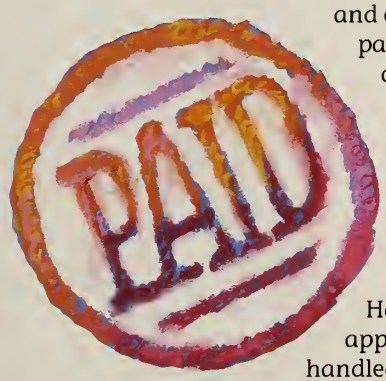

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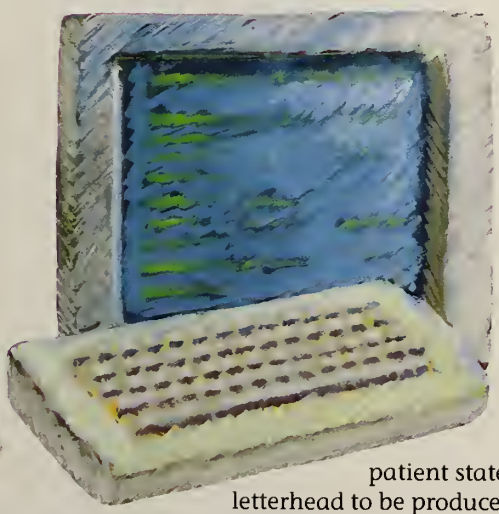

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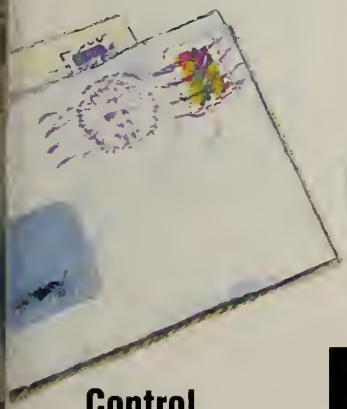

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In Memoriam

Arizona Medical Association

ATKINSON, GEORGE S., Mesa. Died Dec 12, 1989, aged 76. Graduate of University of Arkansas, Little Rock, 1935. Licensed in Arizona in 1964. Dr Atkinson was a member of the Maricopa County Medical Society.

CRAIG, CARLOS C., Phoenix. Died Jan 20, 1990, aged 84. Graduate of University of Illinois College of Medicine, Chicago, 1930. Licensed in Arizona in 1931. Dr Craig was a member of the Maricopa County Medical Society.

CROSBIE, STANLEY B., Phoenix. Died Dec 22, 1989, aged 83. Graduate of University of Minnesota Medical School, 1942. Licensed in Arizona in 1971. Dr Crosbie was a member of the Maricopa County Medical Society.

GRIFFIN, C. CLAYTON, Phoenix. Died Nov 19, 1989, aged 36. Graduate of Tulane University School of Medicine, New Orleans, 1978. Licensed in Arizona in 1979. Dr Griffin was a member of the Maricopa County Medical Society.

OYLER, RAYMOND F., Tucson. Died Nov 17, 1989, aged 84. Graduate of Georgetown University School of Medicine, Washington, DC, 1932. Licensed in Arizona in 1944. Dr Oyler was a member of the Pima County Medical Society.

VIVIAN, CHARLES W., Phoenix. Died Apr 29, 1989, aged 76. Graduate of University of Virginia School of Medicine, Charlottesville, 1944. Licensed in Arizona in 1945. Dr Vivian was a member of the Maricopa County Medical Society.

VOLDENG, KARL E., Phoenix. Died Nov 13, 1989, aged 84. Graduate of University of Iowa College of Medicine, Iowa City, 1928. Licensed in Arizona in 1962. Dr Voldeng was a member of the Maricopa County Medical Society.

Utah Medical Association

BENEDICT, ROLAND DEAN, Blanding. Died Dec 16, 1989, aged 63. Graduate of University of Utah, Salt Lake City, 1951. Licensed in Utah in 1980. Dr Benedict was a member of the Southeastern County Medical Society.

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How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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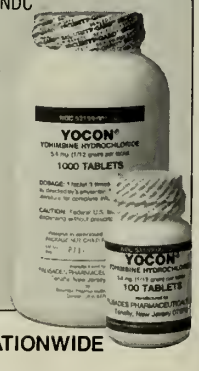

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Reversible confusional states have been observed on occasion, predominantly in severely ill patients.

'Tagamet' has been reported to reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, chlordiazepoxide, diazepam, certain tricyclic antidepressants, lidocaine, theophylline and metronidazole. Clinically significant effects have been reported with the warfarin anticoagulants; therefore, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when 'Tagamet' is administered concomitantly. Interaction with phenytoin, lidocaine and theophylline has also been reported to produce adverse clinical effects.

However, a crossover study in healthy subjects receiving either 'Tagamet' 300 mg q.i.d. or 800 mg h.s. concomitantly with a 300 mg b.i.d. dosage of theophylline (Theo-Dur®, Key Pharmaceuticals, Inc.) demonstrated less alteration in steady-state theophylline peak serum levels with the 800 mg h.s. regimen, particularly in subjects aged 54 years and older. Data beyond ten days are not available. (Note: All patients receiving theophylline should be monitored appropriately, regardless of concomitant drug therapy.)

In a 24-month toxicity study in rats, at dose levels approximately 8 to 48 times the recommended human dose, benign Leydig cell tumors were seen. These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving 'Tagamet'.

A weak antiandrogenic effect has been demonstrated in animals. In human studies, 'Tagamet' has been shown to have no effect on spermatogenesis, sperm count, motility, morphology or in vitro fertilizing capacity.

Pregnancy Category B: Reproduction studies have been performed in rats, rabbits and mice at doses up to 40 times the normal human dose and have revealed no evidence of impaired fertility or harm to the fetus due to 'Tagamet'. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Lack of experience to date precludes recommending 'Tagamet' for use in children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should not be undertaken by patients taking the drug since cimetidine is secreted in human milk.

Adverse Reactions: *Diarrhea, dizziness, somnolence, headache. Reversible confusional states (e.g., mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation), predominantly in severely ill patients, have been reported. Reversible impotence in patients with pathological hypersecretory disorders receiving 'Tagamet', particularly in high doses for at least 12 months, has been reported. The incidence of impotence in large-scale surveillance studies at regular doses has not exceeded that commonly reported in the general population. Gynecomastia has been reported in patients treated for one month or longer. Decreased white blood cell counts in 'Tagamet'-treated patients (approximately 1 per 100,000 patients), including agranulocytosis (approximately 3 per million patients), have been reported, including a few reports of recurrence on rechallenge. Most of these reports were in patients who had serious concomitant illnesses and received drugs and/or treatment known to produce neutropenia. Thrombocytopenia (approximately 3 per million patients) and, very rarely, cases of aplastic anemia have also been reported. Increased serum transaminase has been reported. Reversible adverse hepatic effects, cholestatic or mixed cholestatic-hepatocellular in nature, have been reported rarely. Because of the predominance of cholestatic features, severe parenchymal injury is considered highly unlikely. A single case of biopsy-proven periportal hepatic fibrosis in a patient receiving 'Tagamet' has been reported. Increased plasma creatinine has been reported. Rare cases of fever, interstitial nephritis, urinary retention, pancreatitis and allergic reactions, including anaphylaxis and hypersensitivity vasculitis, have been reported. Rare cases of bradycardia, tachycardia and A-V heart block have been reported with H_2-receptor antagonists. Reversible arthralgia, myalgia and exacerbation of joint symptoms in patients with preexisting arthritis have been reported rarely. Rare cases of polymyositis have been reported, but no causal relationship has been established. Mild rash and, very rarely, cases of severe generalized skin reactions (e.g., Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis and generalized exfoliative erythroderma) have been reported with H_2-receptor antagonists. Reversible alopecia has been reported very rarely.*

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For Whom the Bell Tolls: The Divergence of Hospitals and Physicians

MARCH 1990, VOL. XLVI, No. 3

Marshall B. Block, M.D.

Who would have thought twenty years ago that hospitals and physicians would be at odds? Who would have thought that hospitals would become independent of physicians? Who would have thought that physicians would be in competition with hospitals and no longer support "their' hospital? Well, that's what is happening in the real world in the 1990s. Hospitals and physicians are becoming independent of each other as the revolution in health care reimbursement continues.

For the most part, hospitals were started by physicians but as the hospitals have evolved they have become autonomous with an existence and an agenda of their own. Their future no longer rests with their physician founders but rather with their net income. As such, decisions are being made at corporate levels which do not necessarily reflect the views of their staff members. As health care reimbursement moves from "customary" to capitated, hospitals see their future not with their staff but with their ability to negotiate contracts with third party carriers. In so doing, hospitals need a multi-specialty staff willing to bid for these various programs. This puts the hospital in direct competition with their fee-for-service staff members leading to a greater schism within the medical staff itself. (Hospital versus physician, physician versus physician). Although the hospital needs physicians and physicians need hospitals, their interdependence has been altered by these developments.

Adding further fuel to the fire has been the push for outpatient care which has resulted in the disassembling of hospitals and their resurrection as independent physician owned surgical, radiological and laboratory facilities. Funds generated by these activities were previously in the hospital's domain but are now being shifted to members of the medical staff. Decreasing numbers of admissions for various diagnoses as well as diminishing length of stays for those patients needing admission has produced a frightening drop in hospital income. Thus, "income shifting" and "patient shifting" away from the hospital has made physicians both independent of and therefore less aligned with "their" hospital.

In some communities there is even talk that physicians will be starting their own hospitals, much as it was in the early 40s where physicians owned the hospitals in which they practiced. Obvious conflicts which were present previously would once again arise if such a situation were to occur, especially with our more stringent "conflicts of interest" laws. Nevertheless, as hospitals fight for their survival, various options, such as physician investment in hospitals, are being actively pursued. Physicians are being induced and in some circumstances seduced by economic motives to align with one facility over another.

Where are we going? Where will it end? The current turmoil in physician-hospital relationships is a reflection of the upheaval that is underway in the health care arena. The fallout will be the closing of some hospitals, the restructuring of others, a flight of physicians to salaried positions in group practices aligned with hospitals and/or insurance companies and the alliance of hospitals with the "money players," probably insurance companies as the multitude of "plans" become consolidated into four or five national carriers (CIGNA, Humana, Kaiser, etc.). Ultimately, a division of the "pie" as priorities are set, will result in a universal "net" of basic coverage for all, with options added as dictated by economic factors. The ball has been set in motion, major changes will be here soon.

Marshall B. Block, M.D., Editor

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From Our President

Mark Ivey, Jr., M.D.

One of the most important things a president of any organization can do is to mobilize the membership into action on behalf of important projects or goals.

If nothing else is accomplished during my presidency of ArMA, I hope I can mobilize our membership into a *proactive* stance against the rising costs of health care and cost containment (translation: *rationing)* by our government and third party payors.

Nobody is going to argue the fact that costs have increased dramatically, skyrocketed, mushroomed in recent years. They have. But in our traditional desire to provide medical care to patients instead of providing political leadership to the citizenry, we have allowed medicine to become reactive to the assaults of government, industry and the press concerning the rising costs of medical care.

Friends, the time is past when we can afford to be reactive. We must go on the offensive and let the American public know what we have accomplished and why the cost is high.

First and foremost, we have had a technological revolution in medical care during this generation's lifetime. Even in rural Arizona, CT scanners have become the standard of care. MRIs are ordinary. In less than ten years we have gone from treating acute myocardial infarctions on site in rural hospitals to getting the patient TPA or Streptokinase in the emergency room and flying him to the Mecca for early cardiac catheterization. We no longer even consider obstetrics without ultrasound and electronic fetal monitoring. Endoscopy is everywhere: gastroesophogeal, colon, cystoscopy, ERCP, arthroscopy....even surgery is done "through the 'scope" these days.

All of this is greatly beneficial to the patient. All these things have increased the quality of care. They have also increased the cost of care.

At the same time that technology and new procedures are pushing care costs skyward, the demand for care is increasing just as rapidly. The American public has been trained to expect medical care on demand. Listen to any of the "consumer" groups: Medical care is a "right," right up there with the first ten amendments to the U.S. Constitution.

No one seems to be noticing the fact that increases in cost are as much due to increases in quantity as to increases in quality. Simply stated, there are more sick people being diagnosed and treated. What's wrong with that?

At the recent mid-winter interim meeting of the AMA House of Delegates, a resolution was adopted which, among other things, called for intensive efforts for the AMA "to carry out a factually-based public education campaign clearly delineating the elements of medical care expenditures and explaining the factors leading to unwarranted, unavoidable or unproductive expenses which are not subject to physician control." We didn't invent the population

(Continued on page 11)

During the next several months MICA will answer questions commonly asked about medical malpractice insurance.

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Frequency describes the number of claims reported in a given year. MICA is required by the state to set aside enough funds to cover all our contractual obligations. Severity, the average cost per claim, also impacts our rates. Jury awards and settlements are the major forces driving claim severity.

Recently we have seen a stablization in both the frequency and severity of claims.

MICA hopes the answers to these commonly asked questions will help physicians better understand the complexities of medical malpractice insurance.

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New Directions in Psychiatry

As we enter the last decade of the millennium, these are heady times in psychiatry and related neurobehavioral sciences. Although crystal ball gazing is a hazardous occupation, at the request of the Dean I shall venture onto this thin ice with some personal reflections and perspectives.

An increasing number of windows are opening into the functions and structures of the human brain. Personally, I never fail to experience a sense of awe and wonder when I view an MRI scan. Together with information from PET and other technology, these new imaging techniques are likely to help psychiatry subdivide the many behavioral syndromes that make up our nosology. As heterogenous syndromes like schizophrenia yield to neurobiological dissection, so treatment approaches can become more specific. Advances in genetics also should allow subdivision of diagnostic entities with prospects for future therapeutic advances.

Many major breakthroughs in medical therapeutics have come not from *a priori* hypotheses and laboratory investigation, but rather from serendipitous observations by astute clinicians. So it has been in psychopharmacology, where the last several decades have seen breakthrough after breakthrough--few of which could have been predicted. Much as the recognition of lithium's benefit for patients with manic depressive disease (now called bipolar illness) focused increased diagnostic attention on this major mood disorder, so recent recognition of pharmacologic responsiveness in patients with panic disorder and obsessive compulsive disorder have spurred increased clinician attention and research interest in these conditions. In the 1990s we may see expanded pharmacologic and psychosocial treatments for these and other psychiatric disorders.

Much research in the past decade has focused on means to decrease recurrence rates among the major mental illnesses. The benefits of these studies accrue in decreased mortality, psychosocial morbidity, and economic burdens on families and society. Our own group, for example, found that the use of slightly increased serum levels of lithium can result in dramatic decrements in the risk of a bipolar patient having a manic or depressive recurrence. We are now setting out to try concurrent anticonvulsant therapy and a structured cognitive-behavioral approach in the hope of further lowering this recurrence rate. As this indicates, more research needs to be done to refine existing therapeutic modalities.

Another area of scientific expansion has been in the psychosocial therapies. Long used but inadequately studied, psychotherapies are being standardized and subjected to the same rigorous scrutiny psychiatrists have brought to pharmacologic research. Cognitive and behavioral treatments, in particular, appear to be demonstrating their efficacy in systematic trials.

Important challenges for the 1990s, which we are striving to address at the University of Arizona, include several areas of major public health implications. One is the growing scourge of substance abuse, which afflicts all levels of our population. Not only are new understandings and treatment approaches necessary in general, but patients with major mental illnesses are particularly vulnerable to the hazards of chemical dependency.

A special population in need of research and services is the elderly. As the number of citizens in the upper age ranges expands, psychiatry will be challenged to address the special biological and psychosocial needs of our senior citizens.

Modern advances in our understanding of brain function promise to bring new diagnostic techniques and therapeutic modalities into medical practice. At the same time, they are already destigmatizing mental illnesses, which allows greater focus on public health and medical needs and, in turn, feeds back to increase the visibility of these conditions and funds available to make inroads in their treatment. The University of Arizona hopes to be in the forefront of these exciting new ventures. ■

Alan J. Gelenberg, M.D.

Physician's Health Offers Help, Hope

Denial means never having to say you have a problem. For people whose professional work is deteriorating due to substance abuse or psychiatric or emotional problems, denial is the most common way to avoid dealing with the emotional devastation and the loss of self esteem that facing facts can bring. This is especially true when facing facts means giving up the work that defines identity.

For a physician with a drug or alcohol abuse problem, confronting this disease carries with it the fear of professional discipline, loss of hospital privileges and even the possibility of revocation of the license to practice medicine. Denying the problem seems, subconsciously, the way to preserve the license, the identity, the privileges and life of the physician...preserve, that is, until impaired performance leads to tragedy.

That other choice is the Physician's Health Program, a cooperative effort of the Arizona Board of Medical Examiners (BOMEX), the Arizona Medical Association, the Arizona Board of Osteopathic Examiners and the Arizona State Board of Dental Examiners. The Physician's Health Program involves intervention, interdiction, treatment, counseling and aftercare monitoring.

The program, authorized by the 1986 Arizona Legislature, is funded in part by a surcharge on physician license renewal fees.

During office hours, physicians, colleagues or relatives can call the Medical Director of the Physician's Health Program, Donald L. Damstra, M.D., 249-1302, for information or advice. Also, a 24-hour hotline established by the Arizona State Dental Association at St. Luke's Behavioral Health Center, Phoenix, is now shared by physicians. The hotline, 253-7039, is manned 24 hours a day by a trained nurse who has the ability to handle initial inquiries and refer to the designated physician on call when necessary.

Physicians may enter the Physician's Health Program voluntarily, or they may be referred to the program by BOMEX.

Either way, a discreet investigation and evaluation by trained professionals is done regarding the nature and extent of the physician's addiction and/or other problems which have impaired, or may impair, the ability to effectively care for patients. No action is taken until the evaluation is complete.

At that point, colleagues experienced in chemical dependency or psychological problems intervene, confront the physician and offer treatment for problems identified during the evaluation.

Appropriate therapy, which often involves inpatient or residential treatment, is prescribed. Chemical dependency treatment may include individual or group counseling appropriate to the individual's personal needs. Following residential treatment or outpatient therapy, monitored aftercare continues with counseling and random urine screening.

The program is individually tailored to each physician, but it is designed to prevent substandard patient care while preserving the physician's value as a community resource and actively supporting the physician's recovery. An integral part of the tradition of medicine is that physicians provide help to their colleagues who have alcohol, drug or mental health problems. Because intervention is essential to recovery, many health professionals understand the importance of procuring initial help and intervention for impaired colleagues.

However, aftercare is also a vital part of the recovery process; helping a colleague who has completed an out-of-state residential treatment program connect with the Physician's Health Program aftercare system is also important.

Those who hesitate to help a colleague connect with professional help should remember that reporting a physician to the Physician's Health Program is an act of responsible concern which can save a career--and possibly a life--rather than ending it. It is also required by state law.

By arresting the progress of substance abuse or addictive disease, the Physician's Health Program prevents the ravages to health, family and career which might otherwise ensue, and it prevents harm to the public which might result from the physician's impaired performance.

During its first year, the program started with one group in Tucson and one in Phoenix, with 20 professionals involved. At the present time, 75 medical professionals from all parts of the state are in the program and more than 100 have been involved during the program's three years of existence.

Because the program is still relatively new, Arizona has not yet had time to conduct long-term studies of its effectiveness. However, preliminary results combined with long-range experience of the licensing boards involved suggest a recovery rate around 90 percent--or better. ■

Modifiers—Reaching Optimum Coding Accuracy

Introduction

Today, we will discuss the use of modifiers and how they directly affect the accuracy of your coding and the reimbursement of your services. Modifiers are an essential part of the overall coding process. Without modifiers, physicians would not be able to properly identify their services. Using modifiers with the appropriate CPT-4 code provides you with the means to identify special or unusual circumstances. In the following paragraphs, we will explain how, when and why to use modifiers and how they will affect your reimbursement.

Where to Locate Modifiers

Explanations of the use of modifiers can be found in many places within the CPT-4 coding book. The first place is in the introduction section of the CPT-4 book. Additionally, more descriptive explanations can be found at the beginning of each main section of the CPT-4 book (i.e., medicine, surgery, laboratory/pathology). A listing of all modifiers can be found in Appendix A of the CPT-4 coding book. Becoming familiar with all modifiers will greatly enhance the accuracy of your coding.

Modifiers—(Partial list)

Since there are twenty-two modifiers, we cannot adequately describe each one in this article; therefore, we have chosen a few high impact modifiers to describe in detail. A complete listing of modifiers will be briefly described at the end of this section.

1) 22 - Unusual Services. This modifier should be added to the proper CPT-4 code when the service provided is greater than that usually required.

For example: Multiple diagnosis or extreme age may directly affect the normal pattern of operation. Thus, the use of the 22 modifier would be valid. However, always document the unusual circumstance in the operative note. This will be your only source of documentation for future reference.

2) 50- Bilateral Procedure. This modifier should be used for procedures requiring a separate incision which are performed at the same operative session.

For example: CPT-4 codes 64763 and 64764 include a description for bilateral procedures. Therefore, the 50 modifier would not apply. However, the CPT-4 codes 15820 and 15822 do not include the bilateral description. Therefore, it would be appropriate to use the 50 modifier if both procedures were performed at the same operative session. The 50 modifier would be placed next to the second procedure. For example, 15820 would be submitted without the 50 modifier but 15822-50 should include the modifier. This identifies that it was a bilateral procedure.

3) 51- Multiple Procedures. This modifier should be used when multiple procedures are performed at the same operative session.

For example: A surgeon performs more than one procedure during the same operative session. That surgeon would code the primary procedure as normal. However, the secondary procedure would contain the 51 modifier (identifying it as a secondary procedure). The third and any other procedure should also contain the 51 modifier. It is correct to submit the secondary procedure at 50% of the normal fee and the third procedure at 25% of the normal fee.

Many other factors go into choosing the correct modifier. We recommend that each physician and his or her staff be trained thoroughly before utilizing the modifiers. It is true that there can be too much of a good thing!

(Continued on next page)

Modifiers - (Complete list)

The following is a complete listing of all available modifiers:

- -20 Microsurgery
- -22 Unusual Services
- -23 Unusual Anesthesia
- -26 Professional Component
- -32 Mandated Services
- -47 Anesthesia by Surgeon
- -50 Bilateral Procedure
- -51 Multiple Procedures
- -52 Reduced Services
- -54 Surgical Care Only
- -55 Postoperative Management Only
- -56 Preoperative Management Only
- -62 Two Surgeons
- -66 Surgical Team
- -75 Concurrent Care
- -76 Repeat Procedure Same Physician
- -77 Repeat Procedure Different Physician
- -80 Assistant Surgeon
- -81 Minimum Assistant Surgeon
- -82 Assistant Surgeon (resident not available)
- -90 Reference Laboratory
- -99 Multiple Modifiers

Modifiers

(Continued from previous page)

Reimbursement When Using Modifiers

Since certain modifiers can directly affect the accuracy of your coding, it is important that you use them only when appropriate. Many times insurance carriers will put up "red flags" if a physician submits modifiers on seemingly normal procedures. In contrast, if the service validates the use of the modifier, then by all means use one. A substantial amount of revenue can be lost if a physician does not correctly utilize modifiers. For example, by using the 22 modifier, a physician could appropriately increase his or her fee by 10% to 25% depending on the unusual circumstance.

Summary

Modifiers are the key to optimum coding accuracy. When properly used in conjunction with CPT-4 codes the physician gains control of his or her coding. Not only do modifiers help describe the service in greater detail, but they will also help insurance carriers identify and process your claim more quickly.

Claire Miller and Joan Miller are President and Chief Financial Officer of SysteMedical Management, Inc., a medical practice management firm located in Mesa, Arizona. They can be reached at (602) 833-4855.

Gleanings from the ArMA Past

Bernard L. Wyatt, M.D.
1883-1961

Dr. Wyatt graduated from New York College of Medicine in 1905.

He began practice in Monterey, Mexico, then on to the Bahama Islands 1912-15, thence to France as Associate Director of the Rockefeller Commission in France.

Always on the move, he came to Tucson in the 1920s and in 1926 co-founded the Desert Sanitorium and Institute of Research. He became nationally famous. In 1943 the sanitorium valued at $1 million was given to Tucson to relieve the acute bed shortage, and was converted to the Tucson Medical Center.

In 1929 he founded the Wyatt Clinic in Tucson which became Wyatt-Bensema Clinic and Research Laboratory.

He served on the boards of numerous national organizations, and was a prolific writer on arthritis.

Doctor Wyatt was a mover and shaker.

Dry Gulch Jake

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HIV Blood Test Counseling

adapted from "HIV Blood Test Counseling: AMA Physician Guidelines"

The impact of human immunodeficiency virus (HIV) disease on the health care system is increasing. Although the impact in Utah has not yet been as severe as in other parts of the country, physicians will likely encounter a growing number of concerned individuals and family members who need counseling about possible exposure to HIV.

Although counseling related to HIV antibody testing has been widely recommended,[1-3] the medical literature contains few specific guidelines on how to conduct this counseling. The following provides a brief outline of some essential elements required to conduct HIV antibody blood test counseling.

Pretest Procedures

During the pretest session the patient should be told about HIV, AIDS and other HIV-related diseases, routes of transmission, and methods of reducing the risk of infection. This can be accomplished through a variety of mediums including video/audio-tape, brochures, group lecture, and one-to-one interaction.[4]

The pretest session also must include a patient history of sexual behavior and drug use. The physician should use frank, non-judgmental, open-ended questions to determine the patient's risk of HIV infection. The physician must also be sure that the patient understands the words being used.

Discussing sexual behavior is difficult for many patients and physicians. The interview style and terminology should be tailored to suit the comfort of the patient and physician. The patient's sexual *orientation* is less important than the specific sexual *practices* in which he or she engages.

Discussing drug use also may be difficult. However, information on intravenous drug use and needle sharing is essential. A full drug use history including substances like alcohol and marijuana can also be helpful.

Pretest counseling should include discussion of medical, psychological, and social implications of the HIV antibody blood test. Specific recommendations for behavior change must be based on the physician's assessment of risk. Finally, the physician can help the patient decide whether or not to be tested.

Essential elements of the pretest counseling session include:

- Ask directly why the patient believes he/she needs to be tested.
- Explain that the test determines if antibodies to the virus are present.
- Discuss the meaning of a positive test result: The patient is infected and assumed contagious but does not necessarily have AIDS.
- Discuss the meaning of a negative test result: An individual is not currently demonstrating infection but is not "protected" against the virus.
- Discuss the possibilities of false-positive or indeterminate results.
- Discuss ways to modify behavior to reduce risks.
- Discuss the confidentiality of test results in relation to office/clinic procedures and state reporting requirements (a positive test result must currently be reported to the state health department).
- Discuss potential benefits of anonymous testing.
- Discuss the stress often related to waiting for test results and possible reactions to results (e.g., depression and anxiety).
- Discuss potential negative social consequences of being tested and/or being seropositive (employment, housing, insurance, and personal relationships).
- Help the patient make a decision about testing.
- Obtain consent before conducting voluntary testing.

- Make an appointment for a return face-to-face visit to discuss test results.

Posttest Counseling

Disclosure of the test result is best done at the beginning of the posttest session in a direct manner. Many patients anxiously anticipate the test result and are eager to learn the findings. After the result is disclosed, the patient should be encouraged to express feelings. Repeating the patient'sremarks and labeling his or her feelings can be helpful.

Reporting a positive result can be difficult. If the patient had predicted a positive result during the pretest counseling session, the physician might say, "Well your prediction was right. Your test shows that you have the virus."

Although it is important to be honest and straightforward in reporting a positive result, it is equally important to give the seropositive patient hope. Quoting the annual percentage of seropositive individuals who actually become ill (approximately 7% to 10% per year) and mentioning the ongoing scientific search for effective treatments and vaccines might prove helpful.

The physician must assess the patient's understanding of the result by asking questions such as "Now that you know you are antibody positive (or negative), what does this result mean to you?" The physician must help the patient understand and assimilate the information. A review of information conveyed in the pretest session should be conducted.

When the result is negative, the patient's understanding of how to prevent future infection must be assessed. When the result is positive, the patient must be advised on how to avoid infecting others. He or she must understand that infection is probably lifelong but that having a positive antibody test alone does not mean one has AIDS.

It is also important to communicate to seropositive individuals that they are probably infectious to others by the established routes of transmission and that there is currently no way to predict with certainty when and if clinical symptoms will develop.

Antibody-positive persons should be told:

Do not donate blood, semen, or body organs.

Employ what has come to be known as "safer sex practices," the safest of which is abstention.

Do not share personal hygiene items (e.g., razors, toothbrushes).

Inform physicians and dentists of serologic status.

Encourage sexual partners and needle contacts to seek serologic testing.

The physician must be sensitive to the wide range of psychological reactions possible when the test result is given. Seropositive individuals may react with expression of disbelief, anger, fear, guilt, or self-recrimination. Clinical depression often occurs among those testing positive for HIV antibody.[5-6] In some, the depression may lead to suicidal thoughts or attempts.[7]

Seropositive patients sometimes require repeated sessions, supportive services, and monitoring of psychological functioning. A psychiatric referral should be made for patients who require assistance in adapting to current conditions or managing feelings of depression or anxiety beyond what the primary care physician can offer. A patient may also benefit from counseling hotlines, HIV support groups, and/or psychotherapy. A schedule to monitor medical status must be determined as well.

The posttest session also should include an assessment of the patient's commitment to altering high-risk behaviors. The physician must work with the patient to promote behavior change by reiterating routes of transmission, discussing risks, and highlighting methods of risk reduction.

In summary, essential elements of the posttest counseling session include:

- Provide the test result.
- Allow the patient to express feelings/reactions.
- Assess the patient's understanding of the test results.
- Review routes of HIV transmission.
- Assess the patient's psychological condition.
- Recommend psychiatric follow-up when appropriate.
- Assess risk behavior and commitment to risk reduction strategies.
- Recommend medical follow-up and additional support services as needed.

Conclusion

The need for HIV antibody blood test counseling has been widely acknowledged.[1,2] Physicians must be prepared to provide such services for their patients.

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Pima

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Arizona Health Sciences Center
Dept. of Diagnostic Radiology
George Washington University
School of Medicine - 1987

From Our President

(Continued from page 2)

increase or the fact that there are more older people. We love our elderly and we want them to have excellent health care.

Age is not an illness. But balancing the budget on the backs of our elderly is sick.

And while we're at it, we need to let people know that rationing is, for the most part, no longer performed because of individual cost factors. It's being done through corporate decisions -- often made in other states, in other regions of the nation -- by third party payors (read: insurance clerks). Even worse, major care-cutting decisions are being made by government bureaucrats who are trying to balance the federal budget deficit on the backs of us physicians whose fees have been frozen for years while our expenses, especially liability insurance, have skyrocketed

Now, let me tell you something. When we stop building useless, multi-million dollar MX missiles, when we stop wasting billions bailing out savings and loans, when we get over giving away needless tax moneys overseas, then, we should consider rationing health care at home.

Don't get me wrong. I support cost-effective health care delivery. There is a difference.

Isn't it interesting that the same politicians who are willing to ration care to the elderly are not even remotely interested in rationing their own pay raises?

We have delivered the best health care in the world here in America, and that didn't happen by legislative mandate. Who do you know who went to Canada, England or Japan to get health care that couldn't be provided in the U.S.A.?

The quickest way to diminish the quality of our health care is to let the electorate hear only one side of the problem and be swayed into allowing politicians to practice medicine by legislative fiat. The worst thing we could do as a profession would be to quietly let our bureaucrats interpret these vague, misleading legislative mandates without openly rejecting their intrusions into the patient-physician relationship and responsibility.

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Physicians in the News

Henry Reuss, M.D.

Approximately one year ago Scottsdale gynecologist **Henry Reuss, M.D.**, had an idea -- apply topical Interferon cream in conjunction with laser therapy to prevent recurrence of cervical human papilloma virus (HPV) infection and cervical dysplasia, a precancerous condition

Then Dr. Reuss needed a sponsor. After four months of negotiations he secured the Schering Corporation to sponsor his study. The results of the study will be released some time this spring.

The research involves 40 of his patients diagnosed with dysplasia and HPV, who received laser therapy to treat the infections. A cream was administered following the therapy, applied once each night for eight days. Neither the participants nor the study team know who received the cream consisting of 20 million units of Interferon "A" or a placebo ointment without active medication.

Follow up visits are scheduled for one week as well as one, two, three and four months after laser treatment.

If the recurrence rate is significantly lower or eliminated in the patients receiving the Interferon treatment, then Dr. Reuss's idea works.

In the past year Dr. Reuss treated between 250 and 300 different patients with HPV, a sexually transmitted virus which causes genital warts and has been strongly linked to cervical cancer. Despite laser or cryotherapy, there exists a recurrence rate of 20-30 percent which is on the increase in recent years.

According to Dr. Reuss, the principal investigator of this project, similar studies using Interferon systemically in vulval and vaginal HPV have been performed, but this is the first truly formal FDA-approved study on the cervix.

Dr. Reuss has been in private practice in Arizona for 28 years.

As part of the Phoenix-based Esperanca program, **Paul S. Bergeson, M.D.**, Director, General Pediatric Clinic at Phoenix Children's Hospital, along with others in the local health care field,

William V. Dolan, M.D., Director of Esperanca and Paul S. Bergeson, M.D., Director, General Pediatric Clinic at Phoenix Children's Hospital with their colleagues.

assisted Aparecita Pereira, M.D., a general practitioner, and Jamilse Souza, R.N., both from Brazil, in receiving "hands on" experience to help them better serve the health needs of children from impoverished villages along the Amazon River.

Aparecita and Jamilse were at PCH from mid-October through December 15 making rounds in the wards and nursery, accompanying residents in outpatient examinations, attending teaching rounds with faculty in rotation, and getting exposure to a host of other experiences in a hospital environment greatly more sophisticated and "high tech" than in Brazil.

They also received computer training and additional English at Glendale Community College as part of their educational experience here in the United States. Laptop computers have become an invaluable tool for networking with other countries who share common diseases offering solutions to these and other problems.

For a second consecutive year **Donald J. Ziehm, M.D.,** of the Prescott Women's Clinic presented a paper at the annual meeting of the American Medical Writers Association. Since 1987 one three-hour portion of each meeting has been dedicated to subjects concerning "Progress In Medicine." All members of the Association are invited to submit abstracts. A panel of three editors selects ten papers for presentation at the annual conference and future publication in the Journal of the American Medical Writers Association.

At the 1988 meeting Dr. Ziehm's article dealt with "The Effect of the Malpractice Crisis on the Patient-Physician Relationship." In 1989 in Boston he discussed "Medical Ethics Committees -- The Key to the Future of Medicine?"

Of the approximately 3200 members of the American Medical Writers Association only 354 are physicians. Comprised primarily of professional writers, editors, audiovisual technicians, and public relations and marketing specialists employed in various medical facilities, the Association is committed to strengthening the skills of its members and upgrading the quality of medical writing.

Donald J. Ziehm, Jr., M.D.

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AIR FORCE

The Big Shift!

Watching Congress drive the economy is a lot like being in a car with a teenager learning to drive a stick shift car! The teenager can't quite make a smooth transition from one gear to the next. While changing gears the clutch stutters and the engine almost dies. When the gear engages the teenager presses hard on the accelerator, causing the tires to squeal into action. They then brake too hard and the passengers are flung forward. The poor passengers, their heads spinning and their eyes bulging, just want to stop the car and get out! Congress drives the economy with tax laws. It accelerates with tax incentives. To brake, Congress takes away its tax incentives and taxes and penalizes us on things they used to encourage us to do! I'm sure you have been shaken up and have felt a bit dizzy from all the tax law changes we have experienced.

For some time now we have been in a braking mode. We just about went through the windshield with the 1986 tax act. The real estate market that was zooming down the road got a flat tire, spun out of control, and slammed into a tree. Our wounds are our bloodied real estate portfolios. The hospital bill is the bailout of the S & Ls.

Ken Davis, CPA, CFP

The tax act did a lot of other things too. Pension plan rules were changed to limit how much we could deduct and to spread more of the wealth to our employees. Excessive retirement distributions are now subject to an extra 15% tax. IRA deductions are allowed only to the middle to low income earner. Interest deductions, capital gains tax relief, and the deduction of passive losses were all taken away. Tax rates were reduced, causing us all to steer away from tax incentives even further. Severe penalties were enacted to discourage abusive tax schemes. The brakes were slammed down extra hard this time!

It appears we are about to accelerate and shift gears. The road signs are indicating that some form of savings incentive is just around the corner. A capital gains tax deduction is being pushed. Also, as an alternative, a family savings arrangement is being discussed. This would provide no tax deduction now, but would allow for tax deferral and tax free distribution at retirement. The foot on the gas pedal is slowly bearing down.

The gear change will come as a law to discourage corporate debt and encourage formation of capital through corporate stock issue. This will be achieved by putting stock dividends on an equal footing with interest income. Right now corporations can deduct interest expense but not dividends. This has caused corporations to raise capital by issuing debt instead of equity. Congress is alarmed at the current corporate debt levels. Therefore, it is likely that either dividends will become deductible, or interest expense will become nondeductible, thereby putting both on an equal footing. In the latter proposal, the recipient would get a tax credit for both corporate dividends and interest income received. Both concepts have been proposed already.

The reason for the above changes is that Congress is worried about our low savings rate and our corporations' excessive amount of debt. The government thinks corporations and individuals are all too much in hock. For this reason, I am confident that debt will be discouraged and equity will be encouraged with radical tax law changes.

The results from this kind of tampering will be major. Stock will gain an advantage over bonds, especially if both a capital gains tax deduction is put into place, and a program to encourage equity stock formation such as the credit or deduction program discussed above is put into place. The credit or deduction on dividends would benefit dividend paying stocks over growth oriented stocks. The capital gains deduction would benefit growth stocks and other capital assets like real estate. Preferred stocks and utility stocks may also benefit from dividend credits or deductions.

It is clear that Congress feels strongly about debt and will probably discourage corporate debt and encourage capital formation through issuance of stocks. You may want to rethink the mix of your investment portfolio now before the economic gears change. The hand of Congress is on the gear shift lever and the foot is on the clutch pedal!

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To the Editor:

I have just finished reading the essay on stress by Dr. McGrath in the December issue of *Arizona Medicine*. I find it astounding that this can appear in a journal that purports to represent the opinions of the physicians of Arizona.

This arrogant, paternalistic, medieval judgement upon the sufferers of stress-related disorders blames "wilting softness" of people for their own "self-induced" problems. He manages in four paragraphs to be both strongly sexist (comparing the way fathers used to be so manly and dignified with affluent housewives who are self-indulgent and indecisive) and egotistical (comparing how surgeons and trial lawyers are better than others who are so weak-willed and soft). He blames the experience of stress on incompetence, and feels there would be no stress problems if people just had one thing they could do well. Obviously, so he says, surgeons and trial lawyers can handle the strain because they are all qualified (??), can see their problems selflessly and decisively, and don't experience ambivalence and self-doubt.

How does he explain the multitude (higher rates than the general population) of physicians, lawyers, clergy, and every other profession who suffer stress, and experience alcoholism, addiction, family problems and divorce, suicide, and other emotional problems connected with their interpretation of the world around them as a stressful? Achievement is no protection against low self-esteem. Some of the most dedicated "achievers" are driven out of a base of shame and low self-esteem.

His relegation of group therapy to meaningless flattery, and insistence that people just have to pull themselves up by their bootstraps and just "play the accordion very well" to deal with depression and loneliness is most interesting. Is this current recommended treatment?

I find this diatribe offensive, arrogant, inaccurate, paternalistic, and misleading, and I think it does a terrible disservice to the medical profession since people will look at this and wrongly conclude that it typifies the opinions of organized medicine in Arizona (despite the routine small disclaimer printed beneath your logo four pages earlier).

And let us not forget the health care providers who read this and believe that it is appropriate to treat people suffering from stress-related disorders by telling them to stop their snivelling and pull themselves together; to advise them to merely find something they can do well and their self-doubt and low self-esteem will go away.

The entire spirit and content of Dr. McGrath's writing is insulting to me and I hope to this journal and medical profession. In a time when we are needed to understand our patient's difficulties in coping with their worlds and help them to deal with the low self-esteem, shame, and guilt that underlies their maladaptive behaviors, we are told by Dr. McGrath to act like General Patton in World War II -- figuratively slap them in the face, tell them to stop feeling sorry for themselves, and get back to fighting if they know what's good for them.

Dr. McGrath's article is a slap in the face to good medical care.

Robert L. Elk, M.D.

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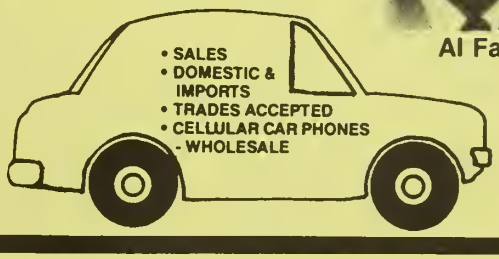

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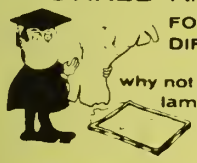

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Clinical Investigation

Serum Antibodies to *Giardia lamblia* by Age in Populations in Colorado and Thailand

EDWARD N. JANOFF, MD, *Denver;* DAVID N. TAYLOR, MD, *and* PETER ECHEVERRIA, MD, *Bangkok, Thailand; and* MARY P. GLODE, MD, *and* MARTIN J. BLASER, MD, *Denver*

We measured levels of antibodies to Giardia lamblia *by age in serum specimens from persons in Denver, Colorado, and Soongnern, Thailand. Serum levels of immunoglobulin (Ig) G, IgM, and IgA* G lamblia*-specific antibodies measured by enzyme-linked immunosorbent assay increased substantially during childhood in both geographic areas, although children in Soongnern showed significantly higher mean levels of each antibody class (P<.05). After adolescence, levels of* G lamblia*-specific IgM fell steadily with age in both populations. In contrast, specific IgA levels remained elevated throughout life among the Thai but decreased to low levels among adults in Denver. Similarly, rates of carriage of* G lamblia *were high among children aged 1 to 4 years in Denver and Soongnern (14.3% versus 26.5%, respectively) but were much lower among adults in Denver (0% versus 14%; P<.01). These data suggest that levels of* G lamblia*-specific IgM may reflect exposure to the parasite early in life in both areas. Levels of parasite-specific IgA may reflect recurrent exposure to* G lamblia *in Soongnern, where* G lamblia *is endemic, but less frequent exposure to the parasite in Denver, where exposure is often episodic.*

(Janoff EN, Taylor DN, Echeverria P, et al: Serum antibodies to *Giardia lamblia* by age in populations in Colorado and Thailand. West J Med 1990 Mar; 152:253-256)

In developed countries, symptomatic *Giardia lamblia* infections occur most often among persons following episodic exposure to the parasite, such as during waterborne outbreaks,[1-3] while backpacking,[4] visiting Colorado mountain towns,[2,3,5] or traveling.[6] Chronic asymptomatic infections with *G lamblia* also occur among persons with recurrent exposure, such as toddlers in day-care centers,[7,8] long-term residents of Colorado mountain towns,[2] and homosexual men.[9,10] In developing countries, recurrent exposure and endemic infections are most common and are often associated with asymptomatic excretion of *G lamblia.*[11-15] The reasons for the differences in the clinical features of *G lamblia* infections in developed and developing countries are not well understood. One proposed explanation is that recurrent exposure to the parasite leads to protective immunity.[2,3,16] The production of antibody to *G lamblia* may be critical to the development of immunity to the parasite since persons with hypogammaglobulinemia show high rates of symptomatic infection with the organism.[17,18] Therefore, because specific antibodies may be important in protective immunity and may represent markers for infection, we compared levels of immunoglobulin (Ig) G, IgM, and IgA antibodies to *G lamblia* by age in persons in a developing area, Soongnern, Thailand, and in a developed area, Denver, Colorado.

Subjects and Methods

Subjects Studied

In the Soongnern district, Nakhon Ratchasima, Thailand, serum specimens were collected in March 1980 from 12 infants born at Soongnern Hospital (cord blood); 135 healthy children in well-baby clinics, schools, and health centers; and 60 healthy adults. In Denver, serum specimens were obtained in 1984 and 1985 from the following urban residents: 13 infants (cord blood), 128 healthy children enrolled in several vaccination trials, and 69 healthy adults. Stool specimens and historical information other than age and sex and place of residence were not available for subjects whose serum was tested. All specimens were preserved at −20°C. Informed consent was obtained from each subject or their representatives in Thailand and the United States.

Serologic Methods

Serum was tested for IgG, IgM, and IgA antibodies to *G lamblia* by the enzyme-linked immunosorbent assay as previously described.[19,20] We used solubilized, axenically grown, *G lamblia* WB strain trophozoites (ATTC No. 30957) as the solid-phase antigen (1 μg per well), diluted the serum 1:100, and applied goat antihuman IgG, IgM, and IgA horseradish peroxidase-conjugated antibodies (Tago, Inc, Burlin-

From the Infectious Disease Section, Medical Service, Veterans Administration Medical Center (VAMC), and the Division of Infectious Diseases, Department of Medicine, University of Colorado School of Medicine, Denver (Drs Janoff and Blaser); the Department of Bacteriology, Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand (Drs Taylor and Echeverria); and the Department of Pediatrics, The Children's Hospital and the University of Colorado School of Medicine, Denver (Dr Glode). Dr Janoff is currently with the Infectious Disease Section, VAMC, and the Department of Medicine, University of Minnesota School of Medicine, Minneapolis.

This work is supported in part by the Veterans Administration Research Service.

Reprint requests to Edward N. Janoff, MD, Infectious Disease Section (111F), VAMC, 1 Veterans Dr, Minneapolis, MN 55417.

game, California) to detect *G lamblia*-specific antibodies. Specimen volumes of 100 μl were tested in triplicate. Each plate was divided equally with serum from age-matched persons from Denver and Soongnern. Results were standardized by adjusting values from each plate to the mean of the sum of the optical densities for seven control serum specimens from all plates. The specificity of the assay was established in preliminary competitive inhibition studies in which the adsorption of specimens of both US and Thai serum for 45 minutes at 37°C on a rotator with 6×10^6 formalin-fixed *G lamblia* WB strain trophozoites resulted in a 50% to 80% decrease in optical density in assays of parasite-specific IgG, IgM, and IgA. In contrast, adsorption with *Cryptosporidium* oocysts and freshly excysted sporozoites (5×10^8; generously provided by Michael Arrowood and Charles Sterling, University of Arizona), *Trichomonas vaginalis* (6×10^6), *Campylobacter jejuni* (10^9), enterotoxigenic *Escherichia coli* (10^9), and *Candida albicans* (10^9) resulted in less than a 12% decrease in optical density.

Parasitology

In Thailand, we determined the prevalence of *G lamblia* infection among 537 healthy Soongnern villagers from stool specimens collected during random visits to their homes. In the United States, stool specimens and questionnaires were obtained from 44 healthy adults in Denver and from 315 children between 12 and 36 months of age, 236 of whom were randomly selected from day-care centers.[21] Stool specimens were fixed in polyvinyl alcohol and in a 10% formalin solution and examined microscopically for intestinal parasites, both directly and after formalin-ether (or ethyl acetate) concentration. In Denver, saline and iodine wet mounts of fresh stool specimens also were examined. Stool specimens from Thai villagers were evaluated by John Cross, PhD, Uniformed Services University of Health Sciences, and specimens in Denver were examined by the Colorado Department of Health, Denver Veterans Administration Medical Center, University of Colorado Medical Center, and Denver General Hospital. Rates of *G lamblia* infection among symptomatic persons in Denver submitting stool specimens for parasitologic evaluation were calculated by reviewing laboratory notebooks for results between 1981 and 1984 at the institutions listed. Stool and serum specimens were collected in the same geographic areas but not from the same subjects in Denver and Soongnern.

Statistics

Mean antibody levels were compared by analysis of variance. Paul F. Smith provided statistical support.

Results

Serology

A pronounced rise in *G lamblia*-specific IgM antibody levels was found during the second through the fifth years of life in both the Denver and Soongnern populations ($P < .001$), but the levels were substantially higher in residents of Soongnern (Figure 1-A). The differences in *G lamblia*-specific IgM levels in residents of Soongnern compared with those in Denver were most pronounced in persons younger than 20 years ($P < .005$), although levels decreased in both populations during the adult years.

Similar to the results for IgM, both populations showed a significant increase in *G lamblia*-specific IgA after the first year of life ($P < .01$ in both groups; Figure 1-B). Although levels subsequently decreased in Denver residents, IgA antibody levels remained elevated in persons in Soongnern throughout adulthood. This persistent elevation in IgA stands in marked contrast to the decline in specific IgM levels in adults in Soongnern, suggesting that *G lamblia*-specific IgA antibodies may reflect recurrent exposure to the parasite. Compared with the Denver residents, Soongnern residents showed a significantly higher level of *G lamblia*-specific IgA

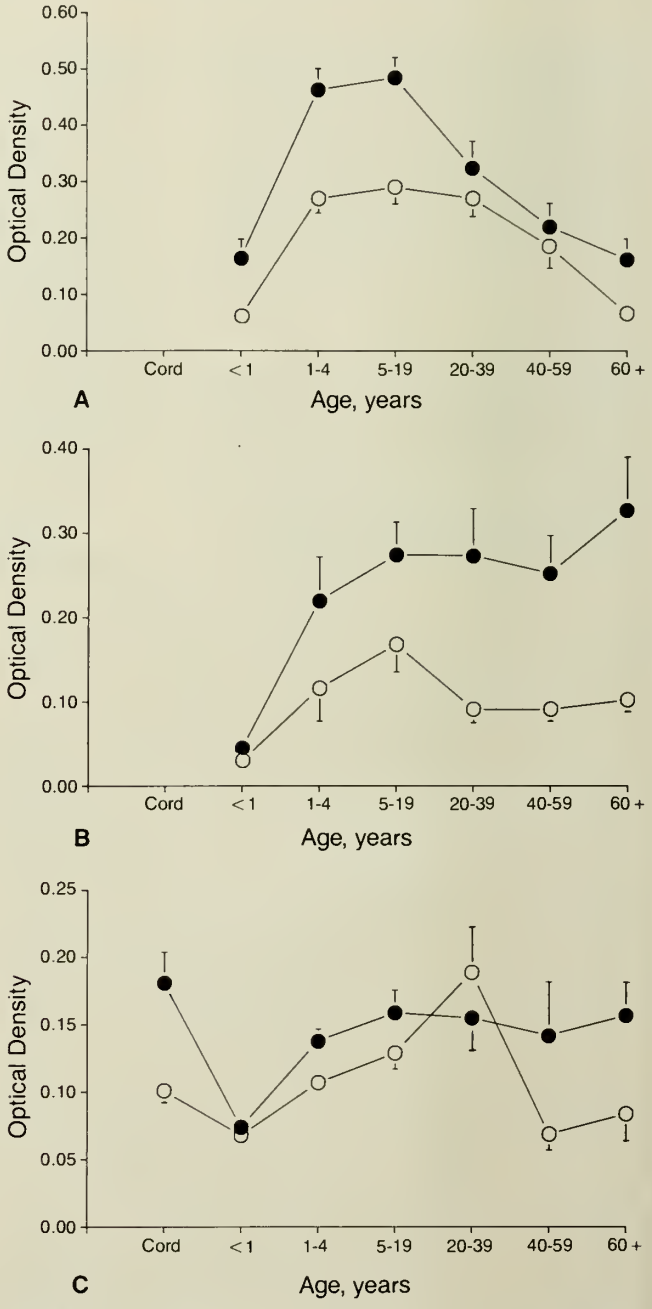

Figure 1.—Age-specific serum antibody levels to *Giardia lamblia* are shown for 210 persons in the United States (○) and 207 Thai villagers (●). Points represent the mean (± standard error) optical density values by enzyme-linked immunosorbent assay for **(A)** immunoglobulin (Ig) M, **(B)** IgA, and **(C)** IgG. The number of serum specimens tested in each age group for the US/Thai populations is as follows: cord blood, 13/12; younger than 1 year, 41/41; 1 to 4 years, 60/60; 5 to 19 years, 35/34; 20 to 39 years, 27/28; 40 to 59 years, 21/20; and 60 years or older, 13/12.

TABLE 1.—*Identification of* Giardia lamblia *in Stool Specimens in Denver, Colorado, and Soongnern, Thailand, 1981 Through 1985*

Location	Age, years	Sample Source	Number Studied	Number With G lamblia (%)
Denver	All ages	Clinical specimens*	10,803	799 (7.4)
Soongnern	All ages	Randomly selected villagers	537	113 (21.0)
Denver	1-4	Randomly selected toddlers†	315	45 (14.3)
Soongnern	1-4	Randomly selected villagers	102	27 (26.5)‡
Denver	20-39	Healthy adults	44	0 (0.0)
Soongnern	20-39	Randomly selected villagers	136	19 (14.0)‡

*Specimens were submitted to the Colorado Department of Health, excluding refugee screening, and to the Clinical Microbiology Laboratories of the University of Colorado, Denver General Hospital, and the Veterans Administration Medical Center, Denver, 1981 to 1984.

†Randomly selected toddlers came from day-care centers (n=236) and non-day-care centers (n=79)—16% and 9% with *G lamblia*, respectively—Denver, 1985 (Novotny et al[23]).

‡Denver population compared with population in Soongnern, $P<.01$.

at all ages ($P<.05$), but the differences were most striking among adults (Figure 1-B).

The levels of *G lamblia*-specific IgG in cord blood specimens from Soongnern, reflecting maternal antibody levels, were significantly higher than from Denver (mean optical density, 0.180 ± 0.02 versus 0.10 ± 0.01; $P<.004$; Figure 1-C). Similar to those of IgM, specific IgG levels were significantly higher in the 1- to 4-year-old group compared with children younger than 1 year in both Denver and Soongnern ($P<.001$). Similar to those of IgA, levels of specific IgG in subjects in Soongnern remained elevated throughout life. Specific IgG antibody levels were highest in persons aged 20 to 39 years in the Denver population and then fell significantly in later life.

Although all data are presented as mean optical density levels, analysis of these data according to median optical density levels or percent of serum specimens above a threshold value produced similar results. No clear bimodal distribution of values was noted in any group. Using a threshold value as a cutoff, more than 80% of Thai adults ($\geq$20 years of age) were seropositive for *G lamblia*-specific IgA compared with less than 20% of adults in Denver.

Parasitology

Giardia lamblia organisms were identified more commonly in randomly selected Thai villagers than among symptomatic Denver residents (Table 1). Among healthy persons in both Soongnern and Denver, *G lamblia* was identified more often in the young children than in adults. Age-related differences in rates of carriage were most striking between adults in the two areas (Table 1).

Discussion

The age-specific levels of antibodies to *G lamblia* in Denver and in Soongnern, Thailand, show similarities in the younger age groups in all antibody classes but notable differences later in life, particularly in specific IgA levels. The early increase in parasite-specific IgM levels in both Denver and Soongnern populations may parallel the intensity of exposure to *G lamblia* early in life. The IgM antibody class is most commonly associated with acute exposure to pathogens, including *G lamblia*.[21] In Denver, the rate of *G lamblia* infection per population is highest in children aged 1 to 4 years,[22] and many urban toddlers excrete *G lamblia* (Table 1).[23] Similarly, in Soongnern, children are more often infected than adults.

The age-related pattern of *G lamblia*-specific IgG and IgA levels is similar in Thais. In contrast to those of parasite-specific IgG and IgM, levels of parasite-specific IgA more clearly distinguish between populations in Soongnern and Denver. Asymptomatic carriage of *G lamblia* is common among adults in developing countries,[14-16,24,25] including in Soongnern where 14% of otherwise healthy adults surveyed excreted the parasite. Rates of excretion of *G lamblia* among healthy adults in the United States are generally much lower (Table 1).[26] During an outbreak of waterborne giardiasis, levels of parasite-specific IgA correlated best with exposure to the parasite,[27] and specific IgA may also best reflect exposure to the parasite in these populations. The parasite-specific IgA detected in serum may be produced systemically or it may originate in part from local intestinal antibody production.[28]

The specific IgG peak in the serum from adults aged 20 to 39 years in Denver corresponds to the peak number of cases of *G lamblia* reported by age in Colorado; 40% of reported cases of *G lamblia* occur in this age group.[22] In the Soongnern population, the IgG pattern by age is comparable to that described in Panama,[29] which suggests a similar pattern of exposure. The degree of protection for infants against *G lamblia* infection from parasite-specific IgG in cord blood is not known. In previous studies, these specimens were tested for antibodies to rotavirus, the heat-labile enterotoxin of *E coli*, Norwalk virus, hepatitis A virus,[30] and *C jejuni*.[31] The results from Soongnern are similar to the patterns for *C jejuni*-specific IgM and IgA in the same Thai population,[31] particularly with the progressive rise in levels of IgA with age, which may reflect ongoing exposure. Similarly, levels of antibody to rotavirus, an infection that causes illness primarily in young children but not in adults, increase early in life in Soongnern residents and remain elevated throughout life.[30]

That *G lamblia* infections in Thai adults are most often asymptomatic whereas in urban US adults, infection often leads to illness may be explained in several ways. Geographic differences may exist in the pathogenicity of *G lamblia* strains.[32,33] High rates of asymptomatic excretion among US day-care-center toddlers[7,8] and homosexual men[9,10] in association with recurrent exposure, however, argue against this hypothesis. Moreover, travelers to developing countries may become ill with *G lamblia* strains acquired in those countries.[6] Alternatively, local intestinal conditions that are conducive to the growth of *G lamblia*[34,35] or to the expression of

virulence factors, similar to those proposed for *Entamoeba histolytica*,[36] may differ in different populations in the two countries. Finally, immunity to the virulence factors causing *G lamblia*-associated illness may develop in persons with recurrent exposure or the strains may mutate on exposure to a specific antibody.[37] In this regard, symptoms were reported in 12 of 14 (86%) Bangladeshi infants newly infected with *G lamblia* but in only 1 of 27 (4%) infected mothers.[25] Moreover, most children in Thailand and Peru with *G lamblia* infection are asymptomatic.[11-13] Antibody to *G lamblia* may be a marker of immunity as parasite-specific levels are elevated in healthy Thai adults and in healthy homosexual men.[19] Antibody to *G lamblia* may be required for immunity as evidenced by the high rates of illness among *G lamblia*-infected persons with hypogammaglobulinemia[17,18] and by the protective effects of *G lamblia*-specific IgA in breast milk.[38]

Levels of parasite-specific IgM may provide a useful tool for determining rates of acute exposure to the organism[19,21,33] in populations. Levels of specific IgA may correlate more closely with recurrent exposure. Continued exposure to the organism is likely required to maintain specific antibody in serum as levels decline steadily over six months following an initial infection (E.N.J., unpublished data, 1986). The ability of antibodies to *G lamblia* to provide protection against *G lamblia*-associated illness by inhibiting adherence,[39] modifying surface antigens,[37] or killing the organism[40,41] remains a stimulating area for investigation.

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Clinical Medicine

Syndrome of Plasma Cell Dyscrasia, Polyneuropathy, and Diabetes Mellitus

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Multiple myeloma associated with sclerotic bone lesions and polyneuropathy represents a distinct subset of the plasma cell dyscrasias. We describe a case of biclonal gammopathy (the second case reported), insulin-resistant diabetes mellitus, and no evidence for anti-insulin receptor antibodies. After treatment with chemotherapy and irradiation, the diabetes resolved, the polyneuropathy lessened greatly, and the patient is alive without evidence of progression five years later. The reports of 95 other cases are reviewed. This syndrome occurs in younger patients (mean age, 48 years) and is frequently associated with organomegaly, endocrinopathies, and skin changes. Irradiation to the sclerotic bone lesions frequently lessens the neuropathy and endocrinopathies and may result in long-term remission. The mechanism of action leading to the systemic effects seen in this syndrome is unknown but is likely related to proteins secreted by the abnormal plasma cells.

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The spectrum of plasma cell dyscrasia is broadening with our increasing understanding of the disease and communication of unusual cases. The bone lesions of multiple myeloma were originally described as entirely osteolytic—"never" giving rise to new bone.[1] These statements were quickly proved wrong with a series of case reports beginning in the 1940s. It is currently estimated that about 3% of all cases of multiple myeloma are of the osteosclerotic type.[2] Now there is recognized a subset of "osteosclerotic myeloma" that is associated with peripheral neuropathy. Patients with this disorder may also have endocrinopathies, including diabetes mellitus.[3] To date, more than 95 cases of plasma cell dyscrasia with peripheral neuropathy and sclerotic bone lesions have been described, including 23 cases with associated diabetes.[3-14]

We report here our experience in treating a patient with plasma cell dyscrasia, biclonal gammopathy, polyneuropathy, and diabetes mellitus to call attention to this unusual syndrome and to add new observations on the pathogenesis of the accompanying diabetes.

Report of a Case

The patient, a 33-year-old man, was seen because of the insidious onset of fatigue, lower extremity weakness, and back pain. He had no history of medication use, toxin exposure, allergies, or diabetes mellitus. He said he did not have impotence. Although he was darkly pigmented, he had not had any increase in pigmentation. There was no family history of diabetes.

On physical examination, his height was 173 cm (5 ft 8 in), his weight was 76.4 kg (168 lb), and his blood pressure was 120/80 mm of mercury. Patellar and Achilles reflexes were absent, and there was lower extremity weakness with the right leg weaker than the left. The patient was unable to stand on his heels or toes. His hands had diminished grip strength, and there was diminished vibratory sensation and poor proprioception in the feet. Skin sensation was normal to pinprick. Tenderness was elicited over the right 12th rib posteriorly. There was no gynecomastia, adenopathy, organomegaly, or peripheral edema.

The initial laboratory evaluation showed a hemoglobin of 173 grams per liter (17.3 grams per dl), hematocrit 0.491 (49%), leukocyte count 8.2×10^9 per liter (8,200 per μl), with differential fractions of 0.55 granulocytes, 0.41 lymphocytes, 0.02 eosinophils, and 0.02 monocytes. Platelets were 250×10^9 per liter (250,000 per μl). No plasma cells were seen in the peripheral circulation. A blood urea nitrogen level was 13.5 mmol per liter (19 mg per dl), and serum creatinine was 88 μmol per liter (1 mg per dl). A Westergren sedimentation rate was 7 mm per hour. A two-hour postprandial blood glucose level was abnormal at 15.3 mmol per liter (276 mg per dl). A five-hour glucose tolerance test with insulin and glucose determination was mildly abnormal. X-ray films showed a sclerotic lesion in the left ilium, a mixed osteolytic and osteosclerotic lesion in the right 12th rib, and small osteolytic areas in the lower right part of L-1 and the lateral part of L-3 (Figure 1). A bone scan showed increased uptake in the 12th rib and symmetrical increased uptake in both sacroiliac joints. A biopsy of the 12th rib revealed a plasmacytoma. Immunoperoxidase stains

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of the biopsy specimen for κ and λ light chains showed diffuse granular cytoplasmic staining using λ antiserum and no staining with κ antiserum. A biopsy specimen of the left posterior iliac crest showed plasma cells morphologically similar to those in the rib, accompanied by an osteosclerotic bone response.

High-resolution serum protein electrophoresis revealed two small paraprotein spikes in the γ region (Figure 2). Total serum immunoglobulins were normal. Immunofixation with reduction showed two distinct monoclonal immunoglobulin G λ proteins that corresponded to the bands within the serum protein electrophoretic channel (Figure 3). Urine immunoelectrophoresis was normal. Cerebrospinal fluid protein concentration was 2.62 grams per liter (262 mg per dl) (normal, 0.15 to 0.45 grams per liter), and electrophoresis showed the two γ paraprotein spikes. Serum growth hormone, thyroxine, prolactin, and albumin concentrations were all normal.

Figure 1.—The x-ray film shows osteosclerotic areas most pronounced in the right 12th rib and left sacroiliac joint.

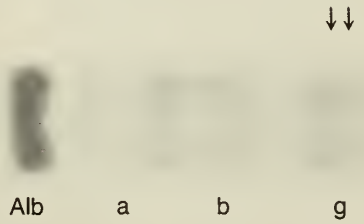

Figure 2.—Serum protein electrophoresis (shown on agar gel) reveals two discrete bands within the γ region (**arrows**).

The painful right 12th rib was irradiated with 24 Gy, and four-day monthly cycles of antimetabolite therapy using melphalan (Alkeran), cyclophosphamide (Cytoxan), and prednisone (Deltasone) were begun.

Four months later (February 1982), the patient was readmitted to the hospital because of a two-week history of flu symptoms that had progressed to blurry vision, polyuria, and polydipsia. Edema to the midcalf was noted bilaterally, and the patient had lost his ability to walk. His fasting blood glucose level was 18.3 mmol per liter (329 mg per dl). Antipancreatic islet cell antibody titers were undetectable. A fasting serum C-peptide concentration was elevated at 10.4 ng per ml (normal is 0.5 to 3.0 ng per ml). Because of reports of anti-insulin receptor antibodies causing diabetes in patients with autoimmune disease, a screening test for anti-insulin receptor antibodies was done.[15] This test is based on the serum's ability to inhibit binding of radioactively tagged insulin to control lymphocytes. No anti-insulin receptor antibodies were detected.

Monthly chemotherapy treatments were continued, and a regimen of insulin, 30 units per day, was begun. In May 1982, seven months after the diagnosis, the sclerotic pelvic lesion was irradiated with 30 Gy. Following this the patient's course gradually improved. His muscle strength increased, and he regained the ability to raise his legs. Insulin requirements decreased despite a 20-kg (45-lb) increase in weight. The insulin therapy was discontinued 13 months after the

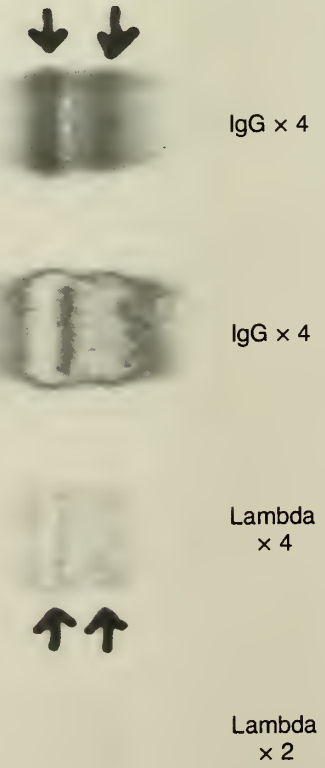

Figure 3.—Serum immunofixation of concentrated immunoglobulin (Ig) G and lambda (λ) shows two distinct monoclonal bands in each (**arrows**).

patient's pelvis was irradiated, and chemotherapy was stopped after 20 monthly cycles.

The patient remains in clinical remission four years later with normal hematologic values and fasting blood glucose concentrations. His muscle strength improved to the point where he can ambulate 12 m (40 feet) without assistance.

Comments and Review

Classic multiple myeloma presents in the seventh decade of life with bone pain, weight loss, fatigue, malaise, and generalized weakness. Anemia, hypercalcemia, and renal insufficiency are often found, the bone marrow is involved by malignant plasma cells, and large amounts of paraproteins are usually apparent in the urine and serum. Lytic bone lesions predominate. The average survival is two to three years.[16]

Plasma cell dyscrasia associated with sclerotic bone lesions and neuropathy is different, occurring primarily at a young age, and patients seek care because of peripheral neuropathy. Anemia, renal insufficiency, and hypercalcemia are uncommon, and concentrations of paraprotein components are small. Patients can survive for many years.

Takatsuki and co-workers first called attention to this unusual syndrome in 1978 when they reported 32 cases.[7] Since then at least 95 cases have been described, including rediscovery of perhaps the first autopsied case reported in 1938 by Scheinker.[17] Bardwick and associates noted several common findings and suggested the mnemonic "POEMS syndrome" for plasma cell dyscrasia with *p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *m*yeloma protein, and *s*kin changes.[3]

We have reviewed 95 cases, which are summarized in Table 1.[3-14,17-38] Criteria for inclusion in this series included the presence of greater than 10% plasma cells by biopsy, bone sclerosis, neuropathy with no other explainable cause (such as amyloidosis or cord compression), and being reported in English.

Patients with this syndrome typically present at a younger age—mean 48 years, range 26 to 67 years. This is significantly younger than those with myeloma in general.[16] The male-to-female ratio in the 95 cases was 76:19. Edema, hirsutism, gynecomastia, ascites, hepatosplenomegaly, and pigmentation changes are sometimes seen. The common clinical findings are summarized in Table 1.

The presenting features of this syndrome are almost always neurologic. Weakness of the lower extremities has been consistently reported, often overshadowing the sensory loss. Diminished or absent deep tendon reflexes occurred in almost all 95 cases, and vibratory sensation and proprioception were frequently absent. The protein levels in cerebrospinal fluid are almost universally high, averaging 2.45 grams per liter (245 mg per dl) at presentation, and papilledema is sometimes present. Nerve conduction studies reveal moderate slowing of motor and sensory conduction. Nerve biopsy specimens show changes of mixed demyelination and degeneration of axon and muscle fibers.[8]

X-ray films in almost all these cases revealed sclerotic lesions that varied in character from pure sclerosis to lytic lesions with surrounding sclerosis. The sclerotic lesions often occurred at sites of ligamentous attachments.[3]

The results of serum protein electrophoresis were normal in 24 of 78 cases. In only a few cases were there larger amounts of paraproteins, more typical of findings in cases of multiple myeloma.[8,11,17-20] Many reports cited "faint" or "small" spikes.[6,10] λ Light chains were reported almost exclusively—rarely were κ light chains found.

Cases of double gammopathy are relatively rare, accounting for only about 2.5% of all cases of paraproteinemia. Double gammopathy occurs most commonly with multiple myeloma and may follow a concordant or discordant pattern.[39] Only one other case of double gammopathy was found occurring with plasma cell dyscrasia and polyneuropathy.[22]

Fasting blood glucose levels were elevated in 23 of 60 patients in whom this value was reported.[3-14] Insulin levels have not been reported. Overt diabetes mellitus developed early in our patient's course. This quickly abated and eventually resolved after radiation therapy for the second sclerotic lesion despite concurrent intermittent treatment with prednisone and a 20-kg weight gain.

In the 95 cases reviewed, there was a "polycythemic tendency" in 41 of 63 patients. When a bone marrow biopsy was done, it revealed only erythrocytosis (11/21). Our patient had a gradual reduction of the hemoglobin from 173 grams per liter to 150 grams per liter after his recovery.

The treatment used in these cases varied. The most consistently successful therapy was irradiation of the osteosclerotic areas. There were 26 cases where radiation therapy was used alone or in combination with chemotherapy and steroids. Of these, 21 patients reportedly respond-

TABLE 1.—*Characteristics of 95 Cases of Plasma Cell Dyscrasia Associated With Sclerotic Bone Lesions, Polyneuropathy, and Endocrinopathy Reported in the English Language Literature**

Abnormal Finding	*Frequency† of Reporting*	*Prevalence Reported, %*
Neurologic		
Paresthesias or weakness	95/95	100
Absent deep tendon reflexes	44/95	46
Absent vibratory sense and proprioception	27/95	28
Papilledema	26/95	27
Endocrine		
Gynecomastia	23/95	24
Impotence	22/76	29
Amenorrhea	3/19	16
Increased pigmentation	43/95	45
Diabetes mellitus	23/95	24
Hirsutism	33/95	35
Other physical findings		
Edema	38/95	40
Ascites	7/95	7
Hepatosplenomegaly or lymphadenopathy or both	37/95	39
Laboratory abnormalities		
Increased cerebrospinal fluid protein concentration	64/95	67
Polycythemia	41/95	43
Abnormal serum protein electrophoresis	54/95	57
Bence Jones proteinuria	9/95	9
Increased erythrocyte sedimentation rate	32/95	34

*From Bardwick et al,[3] Kelly et al,[4] Oavis and Orachman,[5] Oriedger and Pruzanski,[6] Takatsuki et al,[7] Kelly et al,[8] Meshkinpour et al,[9] Waldenström et al,[10] Mayo et al,[11] Rushton,[12] Oelauche et al,[13] Hyman and Westrick,[14] Philips et al,[17] Mangalik and Veliath,[18] Talerman and Bateson,[19] Aguayo et al,[20] Osuntokun et al,[21] Kyle et al,[22] Morley and Schwieger,[23] Iwashita et al,[24] Read and Warlow,[25] Reitan et al,[26] Lowbeer,[27] Rousseau et al,[28] Crow,[29] Courey,[30] Oavidson,[31] Odleberg-Johnson,[32] Getay et al,[33] Castleman et al,[34] Driedger and Pruzanski,[35] Report on a clinicopathological conference held on July 19, 1958, at the Midland Centre for Neurosurgery, Smethwick,[36] Imawari et al,[37] and Trentham et al.[38]

†Frequency is expressed as number of cases in which a finding was present over the total number of cases reviewed.

ed.[3,5,8,13,17,23-26] Our case typifies the dramatic response often seen to all symptoms. The use of prednisone alone was thought to provide improvement in at least eight patients.[3,8,17] Antimetabolite results were poor, with only 9 patients of 29 responding. Many of these were only partial responses or subjective improvements.[6,19,21,26]

Pathogenesis

This syndrome of localized plasma cell dyscrasia with systemic neuropathic and endocrinopathic features strongly suggests that the disordered plasma cells are secreting substances that cause the associated pathologic disorder. This hypothesis is further supported by the fact that the systemic findings are largely alleviated when, as in this case, the bone lesions containing the plasma cells are irradiated.[3,5,8,13,17,23-26]

The neuropathy of this syndrome has been studied the most extensively. Characteristically, there is a mixed sensorimotor deficit beginning distally. Electromyography shows reduced motor-conducting velocities and occasionally signs of denervation.[26] Pathologically, demyelination is present, differentiating this (in addition to the clinical features) from the Guillain-Barré and Eaton-Lambert syndromes.[40(p495)]

Neuropathy has been associated with abnormal monoclonal proteins in varied disorders.[41] Multiple myeloma polyneuropathy has been experimentally reproduced by passively transferring abnormal monoclonal IgG into mice. The Fab fragment was found to reproduce in mice a demyelination similar to that seen in humans.[42] Subsequent studies in humans confirm that monoclonal proteins can be found directed specifically at the peripheral nerve myelin.[43] Although it is tempting to implicate a cause-and-effect relation, more experimental data are necessary before this can be done.[8,43]

The pathogenesis of the diabetes mellitus that occurs in patients with this syndrome has not been investigated. The diabetes, too, may be related to the presence of abnormal plasma proteins. The remission of the diabetes that occurs after successful plasma cell irradiation supports this possibility. The diabetes has the features of type II or insulin-resistant diabetes mellitus. Because rare forms of insulin-resistant diabetes mellitus have been associated with antireceptor antibodies, our patient's serum was screened,[15] but this failed to show any inhibitory effect on insulin receptor activity. Although this finding needs to be confirmed, it strongly suggests that the substance(s) secreted by the abnormal plasma cells in our patient exerted its effect(s) on the postreceptor mechanisms of insulin action rather than on the receptor itself.

Future studies of the biologic effects of paraprotein components would help to clarify the mechanism of action.

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Human T-Lymphotropic Virus Type I (HTLV-I) and Tropical Spastic Paraparesis or HTLV-I-Associated Myelopathy in Hawaii

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Tropical spastic paraparesis or human T-lymphotropic virus type I (HTLV-I)-associated myelopathy is a degenerative encephalomyelopathy with pyramidal tract dysfunction affecting the lower extremities. It is associated with HTLV-I infection and found primarily in the Caribbean region and in southwestern Japan. Five cases of tropical spastic paraparesis (or HTLV-I-associated myelopathy) in Hawaii are reported. All five patients were born in Hawaii; four are women. Each of the patients has parents who were from HTLV-I-endemic areas of Japan. Two of these patients had serum antibodies to HTLV-I. Five of six of the spouses and children of the seropositive patients were also seropositive. Viral cultures of lymphocytes from both seropositive patients and two of the three seropositive children were positive for HTLV-I. None of the five patients had a history of antecedent blood transfusion, multiple sexual partners, or intravenous drug use. There is no evidence of adult T-cell leukemia or lymphoma in any of the patients or their families. Given the increasing seroprevalence of HTLV-I in the United States, clinicians need to be alert to new cases of this disorder.

(Dixon PS, Bodner AJ, Okihiro M, et al: Human T-lymphotropic virus type I [HTLV-I] and tropical spastic paraparesis or HTLV-I-associated myelopathy in Hawaii. West J Med 1990 Mar; 152:261-267)

Tropical spastic paraparesis (TSP) or human T-lymphotropic virus type I (HTLV-I)-associated myelopathy (HAM) is a slowly progressive encephalomyelopathy that generally presents in the middle adult years. The initial symptoms are increasing difficulty in walking, low back pain, and cramping sensations of the legs. Urinary sphincter dysfunction is also common. Impotence or diminished libido is almost universal. Most cases reach a clinical plateau within two years of the start of symptoms and remain at that level of function, without remission, for years.

Groups of patients with this disorder have long been recognized in southern India, Jamaica, South Africa, and Colombia.[1-4] The geographic clustering and sporadic appearance of this neurologic syndrome led to the finding of both epidemic and endemic forms of the disease. Epidemic forms followed increased ingestion of vegetable toxins in the context of malnutrition and regional drought.[5,6] Clues to the origin of the endemic form remained unclear, however, until antibodies to HTLV-I were found in the blood of ten patients with TSP/HAM in Martinique.[7] Seropositivity to HTLV-I was subsequently confirmed in a number of Jamaican and Colombian patients with the syndrome, and, in addition, antibodies to HTLV-I were found in their cerebrospinal fluid.[8]

Soon afterward, patients living in nontropical areas of southwestern Japan, which are endemic for HTLV-I and adult T-cell leukemia or lymphoma (ATLL), were independently reported to have the same chronic, slowly progressive spastic myelopathy. Serum from these patients was also positive for HTLV-I antibodies.[9] This syndrome in Japan was termed "HTLV-I-associated myelopathy." Subsequently, cases of tropical spastic paraparesis or myelopathy associated with HTLV-I have been reported from Trinidad and Tobago,[10] Ivory Coast,[11] Colombia,[12,13] the Seychelles islands,[14] West Indian-born residents in the United Kingdom,[15] France,[16] Italy,[17] Peru,[18] and from the United States.[19]

Pathologic evidence clearly linked the Caribbean form with the Japanese form of spastic paraparesis. The primary changes are astrocytic gliosis, capillary proliferation, perivascular lymphocyte cuffing, and loss of both myelin and axons in the pyramidal, spinocerebellar, and dorsal columns of the spinal cord. Similar but less striking changes are found in the medulla, pons, and in the white matter of the cerebellum and cerebrum of these patients.[20]

Because of confusion over the nomenclature, a consensus panel at the 1989 World Health Organization HTLV-I meeting in Kagoshima, Japan, determined that the diseases,

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ABBREVIATIONS USED IN TEXT

ATLL = adult T-cell leukemia or lymphoma
ELISA = enzyme-linked immunosorbent assay
HAM = HTLV-I-associated myelopathy
HIV = human immunodeficiency virus
HTLV-I = human T-lymphotropic virus type I
TSP = tropical spastic paraparesis

tropical spastic paraparesis and HTLV-I-associated myelopathy, are identical and formally proposed that the syndrome be called "TSP/HAM."[21]

Persuasive evidence for a closer association of disease and virus came with the isolation of HTLV-I from cerebrospinal fluid lymphocytes of a patient in Japan with TSP/HAM who had both serum and cerebrospinal fluid HTLV-I antibodies.[22] Subsequent work using electron microscopy has shown HTLV-I-like viral particles in pathologic spinal cord tissue from a Jamaican patient with TSP/HAM.[23] Intact HTLV-I virus has been produced using peripheral lymphocytes from healthy controls cocultured with irradiated T-lymphocyte cell lines derived from patients with TSP/HAM.[24] Southern blot hybridization of cultured T lymphocytes from cerebrospinal fluid of patients with TSP/HAM has revealed HTLV-I in a proviral form in these cells. Electron microscopy has shown type C retroviral particles in the same cultured cells.[25] Intrathecal synthesis of HTLV-I antibodies and oligoclonal bands in cerebrospinal fluid specimens of TSP/HAM patients from the Caribbean region and West Africa has also strengthened the evidence for the causal relationship between HTLV-I and TSP/HAM.[26]

At the molecular level, specific DNA sequences of HTLV-I isolated from patients with HTLV-I-associated myelopathy were found to be homologous on DNA blotting to sequences from patients with adult T-cell leukemia or lymphoma.[27] Atypical lymphocytes with lobulated nuclei similar to the atypical lymphocytes in the blood of patients with ATLL are found in the peripheral blood and cerebrospinal fluid of patients with TSP/HAM.[28] To date, only one patient has been reported who had both HTLV-I-associated diseases: he was a Trinidadian man who had TSP/HAM for 16 years before adult T-cell lymphoma developed.[10]

Evidence for HTLV-I transmission points to three primary routes: sexual transmission, most frequently from male to female through the leukocyte component of semen[13,29,30]; mother-to-infant transmission through breast milk[29,31,32]; and direct transmission by blood transfusion[33-37] as well as by sharing needles in intravenous drug use.[38] Although lymphocytes containing HTLV-I have been found in the umbilical cord blood of a baby born of an HTLV-I-positive mother, in utero transmission is unusual.[39] Data from Okinawan residents, Okinawan immigrants to Hawaii, and their Hawaiian-born offspring implicate the importance of intimate household contact (sexual as well as breast-feeding routes) in the transmission of this virus.[40] The transmission of HTLV-I differs from that of the human immunodeficiency virus (HIV) in that for HTLV-I to be transmitted, it must be in an intracellular form. Recipients of lyophilized factor concentrates did not seroconvert to HTLV-I as they did to HIV.[41]

The possibility that mosquitoes or other hematophagous insects may be HTLV-I vectors is unlikely but is still unresolved.[42,43] The role of cofactor parasites is also uncertain.[42,44] Environmental antigenic stimulation, parasitic or otherwise, has been proposed as a mechanism of activation of latently infected helper T lymphocytes or proviral states (including "smoldering ATLL") which then may develop into clinical TSP/HAM or ATLL.[40,42]

It is not clear why most antibody-positive persons remain asymptomatic while in a few TSP/HAM (or ATLL) develops. Recent evidence from human leukocyte antigen screening of HTLV-I-endemic areas in Japan indicates that there is a relationship between specific HLA haplotypes and persons in whom either TSP/HAM or ATLL develops, suggesting genetically determined HTLV-I disease susceptibility.[45]

Antibodies to HTLV-I are present at a rate of 0.2% in the healthy, volunteer blood donor population in Hawaii (J. Frohlich, MD, Blood Bank of Hawaii, oral communication, February 1989). Adult T-cell leukemia or lymphoma associated with HTLV-I serum antibodies has been reported in Hawaii,[46,47] but heretofore not TSP/HAM.

Given the presence of ATLL and the background level of HTLV-I seropositivity, we postulated that TSP/HAM was present in Hawaii and that it would be associated with HTLV-I infection.

Patients and Methods

Patients

From a survey of four neurology practices in Honolulu, a group of patients with unexplained spastic myelopathy was selected. Five of these patients were found to have tropical spastic paraparesis or HTLV-I-associated myelopathy on the basis of an interview, neurologic examination, and a review of their medical records. Criteria for TSP/HAM in this study are a slowly progressive clinical course reaching a steady state of neurologic impairment over one to two years and having no remissions, primary pyramidal tract signs including bilateral lower extremity weakness and spasticity, no evidence of other neurologic disease (including dementia), and no myelographic evidence of spinal cord compression.[48-50] There was no history of blood transfusions, intravenous drug use, or homosexual or nonmonogamous heterosexual activity in any of the patients found to have TSP/HAM or in their family members.

Volunteer blood donors at the Blood Bank of Hawaii were used as a control population to determine the background rate of HTLV-I seroprevalence in this area. Because all five patients with TSP/HAM are of Japanese descent and because specific areas of Japan have high rates of HTLV-I seropositivity, only serum from Hawaiian blood donors of Japanese ancestry was used to more closely match the patients reported in this study. The rate of overall HTLV-I seropositivity in blood donors in Hawaii is 0.2%. The rate of HTLV-I seropositivity in blood donors of Japanese descent in Hawaii is 0.8% (J. Frohlich, MD, Blood Bank of Hawaii, oral communication, February 1989).

Laboratory Tests

A complete blood count was done on each patient with TSP/HAM. Serum specimens from each of the patients and 17 of their immediate family members or close relatives were tested in duplicate using the Biotech/Dupont HTLV-I enzyme-linked immunosorbent assay (ELISA) kit (Wilmington, Delaware). This kit uses detergent-disrupted

HTLV-I virions produced in a HuT-102-2B T-lymphocyte cell line. Positivity was determined by establishing a cutoff absorbance value (at 410 nm). The cutoff was set at 60% of the mean absorbance of three positive control serum specimens. Any specimen whose average absorbance was greater than the cutoff was deemed positive.[51]

All ELISA-positive results and ELISA-negative results on serum specimens of TSP/HAM patients were confirmed by Western blot. The Biotech Western blot test kit (Rockville, Maryland) for HTLV-I was used. This kit uses nitrocellulose strips onto which HTLV-I-specific polypeptides have been electrophoretically blotted. Specifically bound human immunoglobulins to HTLV-I antigens such as p19, p24, p28, p36, and gp46 are visualized by a goat antihuman immunoglobulin biotin conjugate and an avidin horseradish peroxidase conjugate with 4-chloro-1-naphthol substrate. The presence of HTLV-I antibodies in a patient's serum is indicated by in situ bands representing specific HTLV-I antigens. Serum that was reactive with both p19 and p24 was considered to contain HTLV-I antibodies.

All patients with ELISA-positive serum and their seropositive family members were tested for culturable HTLV-I virus. Heparinized peripheral blood leukocytes from these persons were banded in a solution of Ficoll and diatrizoate (Hypaque) and stimulated with phytohemagglutinin P at 5 μg per ml for two to four days. The mitogen was then removed and the cells cocultivated for as long as ten weeks with an equal number of phytohemagglutinin-stimulated mononuclear cells from human umbilical cords. Culturing was done in RPMI 1640 with a 20% solution of heat-inactivated fetal bovine serum and 10% interleukin-2 (Cellular Products, Buffalo, New York). Periodically, fresh cord blood cells were added when necessary to maintain a culture. Several times during the cocultivation process, cells were placed on slides, fixed with a 1:1 solution of methanol and acetone, and tested for the expression of HTLV-I p19 and p24 by reaction with monoclonal antibodies specific for those antigens. The reaction of the antibodies with the cells was detected by the alkaline phosphatase, antialkaline phosphatase immunocytochemical procedure.

Results

Five Hawaiian patients were found to meet the clinical criteria for tropical spastic paraparesis or HTLV-I-associated myelopathy. Each of these patients was born in Hawaii and has lived there for his or her entire life. The parents of these patients were all born in Japan. Each parent emigrated to Hawaii before age 20 and before marriage. Four patients are married women and one is a single man. There is no history of an antecedent blood transfusion, intravenous drug use, or multiple sexual partners in any of the patients. All of the patients were breast-fed as infants. They range in age from 46 to 71 years (mean, 58.4 years). The age at which symptoms first started ranges from 36 to 52 years (mean, 41.6 years). Symptoms have lasted from 7 to 32 years (mean, 16.8 years) in the five patients.

The first symptom of clinical disease in each of these patients was leg weakness, most noticeable as difficulty going down stairs and early fatigue on walking distances. Other early symptoms in this patient group were lower extremity dysesthesias and muscle spasms. As the disease progressed, patients reported increasing awkwardness of their gait and, later, falling due to leg weakness. Several reported difficulty in getting out of bed in the morning because of "muscle stiffness." All five patients had urinary incontinence of a variable degree. There has been no remission of signs or symptoms in any of these patients. None of these patients has any intellectual impairment. The present degree of physical disability ranges from needing a cane for ambulation (two patients), to requiring a walker (two patients), to being completely wheelchair bound (one patient). Three have had hip fractures following falling.

None of the patients has any evidence of upper extremity involvement by examination. Two patients do, however, have upper extremity dysesthesias. All patients have hyperreflexic knee and ankle jerks with extensor plantar reflexes bilaterally. Three have clonus at the ankle. Quadriceps and hamstring muscle tone shows considerable spasticity but is fairly symmetric in all patients. All patients have a variable degree of weakness in the lower extremities, with the anterior tibialis muscle group being most affected. Sensation to temperature and pinprick is normal in all patients. Three patients have decreased vibratory sensation at the level of the metatarsals. Examination of the gait shows a mild to moderate foot drop, difficulty lifting the knees, and pronounced scissoring (one patient was unable to ambulate). Gait rhythmicity was irregular. Stopping and turning required more effort and concentration than normal. Cerebellar function was intact in the upper extremities in all patients: it was difficult to assess in the lower extremities because of spasticity and weakness. Other neurologic findings are summarized in Table 1. Myelograms of each of the five patients were normal. Hemoglobin concentrations, hematocrits, and leukocyte and differential cell counts were normal in all patients. A VDRL test for syphilis was negative in all patients.

There was no significant difference clinically between the seropositive and the seronegative patients. The seropositive patients were neither the most nor the least seriously affected of the five patients with tropical spastic paraparesis.

The only medications taken frequently by several of these patients were muscle relaxants, which were used on a symptomatic basis. Antihypertensive and thyroid supplement medication were each taken by one patient in this group. None of the patients had ever been treated with steroid, immunosuppressive, or immunomodulatory medications.

Two of the five patients with TSP/HAM are HTLV-I antibody-positive. The serologic results from the five patients and their relatives are presented in Figure 1. The results of Western blot confirmation of the ELISA-positive persons are shown in Figure 2. In each case, the Western blot test confirmed the result of the ELISA tests done on these seropositive patients. Western blot tests on the seronegative patients were negative for all bands.

Antibody titers are shown in Table 2. There is excellent serologic correlation among the three HTLV-I-negative patients (patients 1, 2, and 3) and their family members: all spouses, siblings, and offspring tested are seronegative. All three of the seronegative patients had parents who were born in HTLV-I-endemic areas of Japan.

The correlation among the two seropositive patients (patients 4 and 5) and their families is nearly as strong. Each of the spouses is seropositive. Three of the four offspring tested are also seropositive. (A single offspring was unavailable for testing.) The 82-year-old mother of patient 4—born in an

endemic area of Japan and immigrated to Hawaii at 16 years of age—is seronegative. Four of ten living siblings of patients were tested, and one of these is seropositive. Although not examined, the seropositive sibling (female) reported progressive leg weakness and gait instability. The spouse of that seropositive sibling is seronegative.

Figure 3 shows the results of HTLV-I viral cultures using peripheral lymphocytes from the seropositive patients with TSP/HAM and their seropositive family members. Patient 4 and her two seropositive offspring are culture-positive. Her spouse, who is also seropositive, is culture-negative. Patient 5 is culture-positive for HTLV-I. Both her seropositive spouse and her seropositive offspring are culture-negative. As a negative control, lymphocytes from patient 3 (seronegative) were cultured using the same methods; he was culture-negative for HTLV-I.

Activated, ATLL-like, atypical lymphocytes with polylobulated, cerebriform nuclei were seen on the peripheral smears of both seropositive patients (Figure 4). The spouse of patient 5 also had ATLL-like lymphocytes on his peripheral smear. In patient 5, polylobulated nuclei are present in approximately 10% of her peripheral lymphocytes. In the other two persons, similar nuclei were seen in fewer than 5% of the lymphocytes on their peripheral smears.

Discussion

These data indicate that tropical spastic paraparesis, or HTLV-I-associated myelopathy, a neurologic syndrome found in many areas of the world, is present in Hawaii. Unique to this location are the elements of tropical spastic paraparesis found in the Caribbean region and of HTLV-I-associated myelopathy in southwestern Japan. Hawaiian TSP/HAM exists in a tropical environment (unlike in Japan), but in Hawaii it is found in the immediate descendants of Japanese migrants from HTLV-I-endemic areas (in the pattern of Japanese familial transmission). There is no differ-

TABLE 1.—*Clinical Summary of Patients With Tropical Spastic Paraparesis*

				Symptoms				Neurologic Signs			
Patient	Age, yrs	Sex	HTLV-I Serologic Results	Age at Onset, yrs	Early	Later	Bladder	Vibratory at Toes	Knee Reflexes	Ankle Reflexes	Gait
1	68	♀	Neg	36	Leg stiffness; spasms	Dysesthesias; falling	Incontinence	Decreased	Hyperreactive	Clonus	Stiff, awkward; foot drop; scissoring; requires walker
2	46	♀	Neg	39	Leg weakness	Low-back aches	Frequency	Normal	Increased	Clonus	Stiff; foot drop; scissoring; requires cane
3	48	♂	Neg	38	Leg weakness; unsteady gait	Leg cramps, spasms; dysesthesias, falling	Incontinence	Decreased	Hyperreactive	None	Unable to stand; contractures; wheelchair bound
4	59	♀	Pos	52	Leg weakness; unsteady gait	Low-back pains; leg cramps	Incontinence	Normal	Increased	Hyperreactive	Awkward; foot drop; mild scissoring; requires cane
5	71	♀	Pos	43	Leg weakness, aches	Wavering gait; leg cramps	Incontinence	Decreased	Hyperreactive	Clonus	Stiff, halting; foot drop; scissoring; requires walker

HTLV-I=human T-lymphotropic virus type I, Neg=negative, Pos=positive

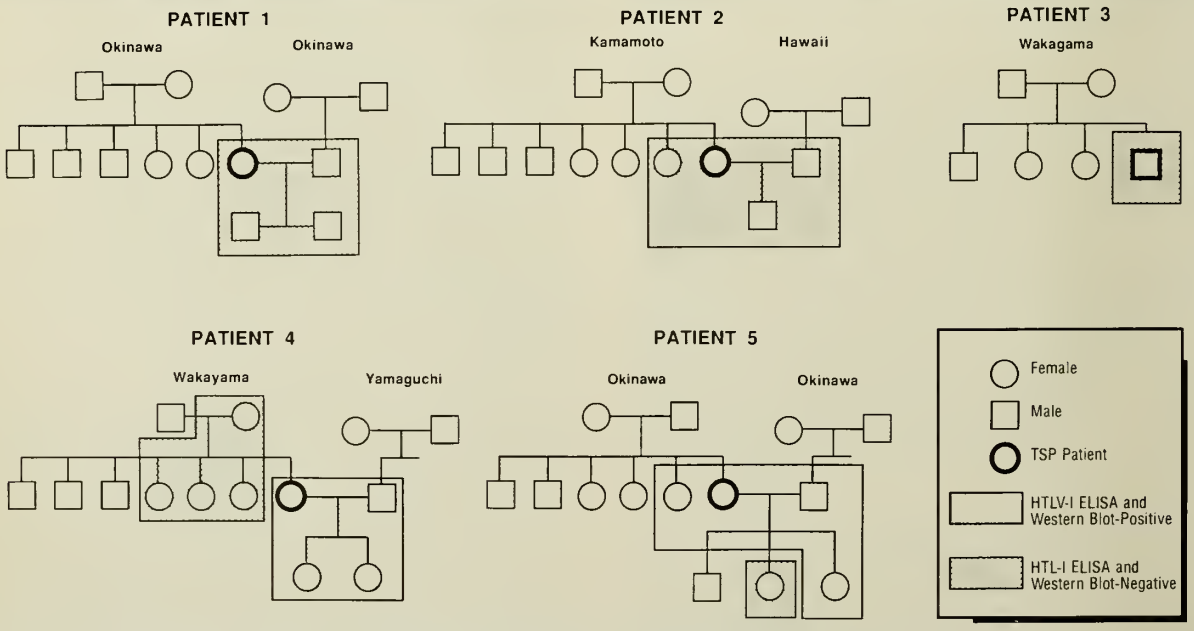

Figure 1.—The pedigree chart shows the city or state of birth and the distribution of the human T-lymphotropic virus type I (HTLV-I) in the families of the patients with tropical spastic paraparesis (TSP). ELISA = enzyme-linked immunosorbent assay

ence in the signs, symptoms, or prognosis between these two syndromes; they are the same disease.[21] Postmortem pathologic evidence bears out these similarities.[20] Neither name is optimal because patients with this disease are found in nontropical areas (southwestern Japan) and not all patients with the clinical disease are seropositive (which is a requirement of HAM in Japan); thus, "TSP/HAM" is a good compromise.

The familial virus clustering pattern reported in highly endemic areas is present in the seropositive families described here. Viral clustering of HTLV-I, as found in Hawaii, includes parents and their children. Parental siblings living in other households, however, do not share the same high rate of seropositivity as do household members.

These data do not pinpoint specific modes of transmission in Hawaii, but they indicate the importance of close familial contact in viral transmission. Both vertical and horizontal routes of transmission, common to other HTLV-I-endemic areas, probably occurred in the families described in this report. In the case of patient 5, transmission may have been either vertical, through breast milk from her mother (from an endemic area), or horizontal, through male-to-female sexual transmission from her seropositive spouse who has a very high antibody titer and whose parents are also from an HTLV-I-endemic area. If the latter is the case, this may explain why the eldest offspring of this family is seronegative: at the time of the birth of this first child, patient 5 may not have been infected with HTLV-I or, if infected, she may not have had a high enough viral titer at that time to effectively transmit HTLV-I to her first infant.

In the case of patient 4, whose parents are from an endemic area but whose spouse's parents are from an area of low seroprevalence in Japan, the transmission of virus to both children was most likely through breast milk. The spouse of patient 4, who had a low antibody titer, may have been exposed to the virus through female-to-male sexual transmission from his seropositive wife. This is an uncommon route of HTLV-I transmission in Japan, although it may be analogous to the female-to-male transmission of HIV type 1 seen in other areas of the world. It is also possible that even though his mother was from an area of low seroprevalence, she was HTLV-I-positive and he was infected by the breast-milk route.

Three of our patients were seronegative. Approximately one of four TSP/HAM patients in the Caribbean region is seronegative, but few Japanese patients having the full clinical syndrome are seronegative (M. Osame, MD, Kago-

TABLE 2.—*Human T-Cell Lymphotropic Virus Type I Antibody Titers in Seropositive Families*

Patient and Family Member	*Results of ELISA and Western Blot Tests*	*Antibody Titer*	*Virus Culture*
Patient 4	Pos	1:2,560	Pos
Spouse	Pos	1:320	Neg
Offspring	Pos	1:640	Pos
Offspring	Pos	1:640	Pos
Patient 5	Pos	1:2,560	Pos
Spouse	Pos	1:20,480	Neg
Offspring	Pos	1:80	Neg

ELISA=enzyme-linked immunosorbent assay, Neg=negative, Pos=positive

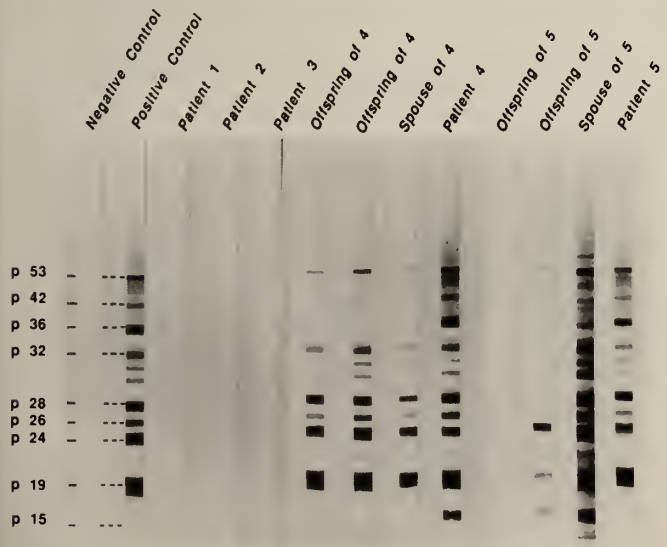

Figure 2.—The Western blot results are shown for the patients with tropical spastic paraparesis and their seropositive family members.

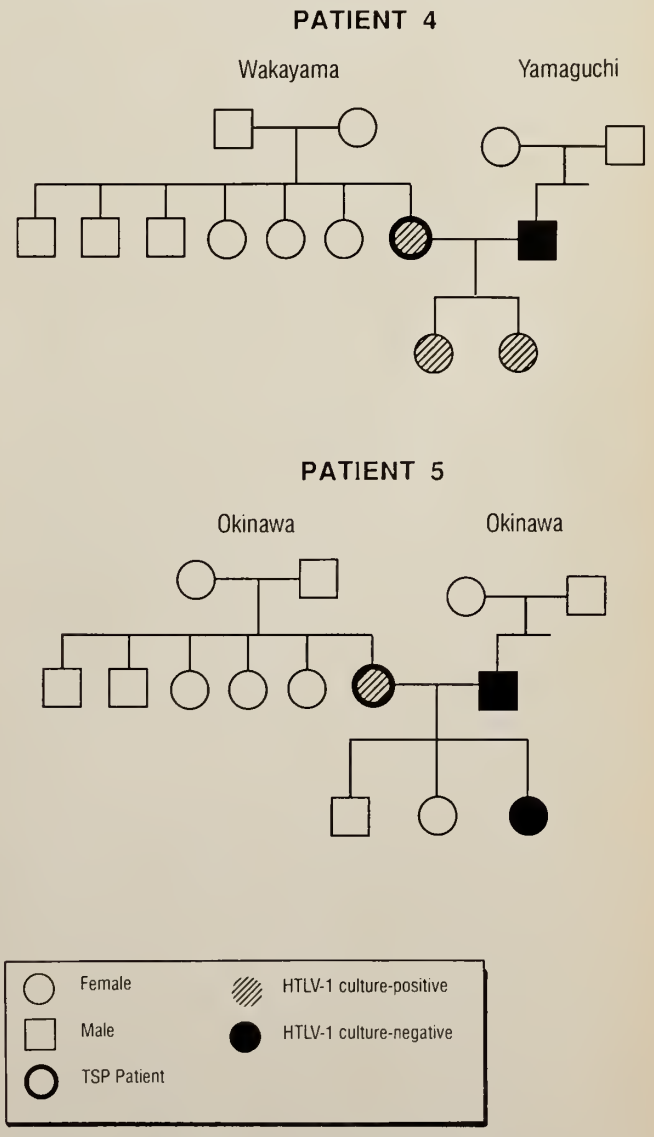

Figure 3.—The charts show the results of the cultures for human T-lymphotropic virus type I (HTLV-I) in patients 4 and 5 and their siblings and spouses. TSP = tropical spastic paraparesis

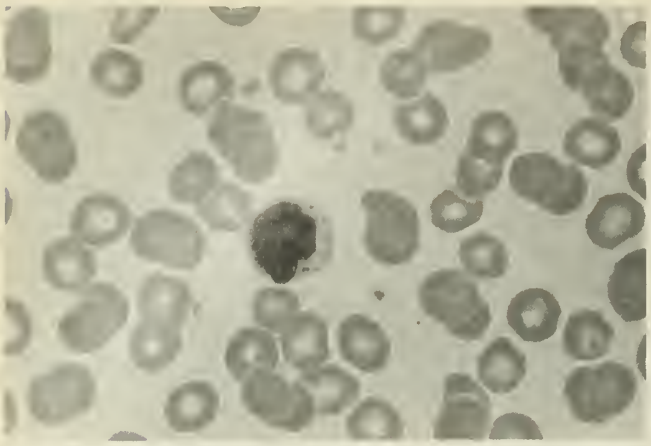

Figure 4.—A representative atypical lymphocyte is seen on the peripheral blood smear of patient 5 (Wright's stain, original magnification × 1,000).

shima, Japan, oral communication, February 1989). In a recent study, only two of eight patients with TSP/HAM from the United States were found to have antibodies to HTLV-I.[19] It may be that, in seronegative patients, the virus is present but serologically silent in a proviral form. It will be important to study seronegative patients with TSP/HAM for HTLV-I infection using more sensitive techniques including the polymerase chain reaction and more extensive attempts at viral culture. It may also be that a second virus may cause a clinically similar disease.

These cases of TSP/HAM are among the first described in citizens of the United States. Both TSP/HAM and ATLL represent patterns of HTLV-I disease not commonly seen in this country. With the increasing prevalence of HTLV-I noted in intravenous drug users in this country and with the finding of patients with leukemia who seroconverted following multiple blood transfusions in New York City,[52] there is reason to anticipate that TSP/HAM will develop in some of the recipients of these blood transfusions in endemic regions of the US. In addition to transfusion recipients, intravenous drug users, their sexual partners, and their breast-fed infants are other groups at risk of having TSP/HAM. As seen in Hawaii, persons whose parents emigrated to the US from HTLV-I-endemic areas are also clearly at risk of TSP/HAM or ATLL developing. To date there are no reports of cases of ATLL in Japan or in the US that have resulted from transfusion.[53] Given the long latency between HTLV-I infection and the development of ATLL, transfusion-associated ATLL will be difficult to identify.

To protect the US blood supply and the noninfected, recipient population as a whole, epidemiologic information needs to be obtained to determine which areas and which subgroups in the United States have the highest rates of HTLV-I infection. Routine screening of donor blood in these areas will limit iatrogenic HTLV-I transmission and reduce the rate at which HTLV-I is introduced to this country.

Because of the particularly long latency period of HTLV-I infection, the potential scope of this problem is difficult to assess in the absence of seroprevalence information at the national level. An additional factor in estimating the magnitude of possible clinical disease is the question of whether those persons infected with both HIV and HTLV-I will be more likely to have TSP/HAM or ATLL or whether immunodeficiency will develop and they will succumb to the acquired immunodeficiency syndrome first. Clinicians need to be aware of TSP/HAM in patients presenting with spastic paraparesis and that TSP/HAM provides a different model for the study of retroviral infection of the central nervous system.

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Medical Progress

Chronic Urticaria

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Urticaria affects 15% to 20% of the population once or more during a lifetime. Chronic urticaria is a frequent recurrent eruption over a period greater than 6 weeks; the cause remains a mystery in more than 75% of cases. Urticaria and angioedema may be produced by immunologic or nonimmunologic means. Urticarial vasculitis, contact urticaria, mastocytosis, physical urticarias, dermatographism, cholinergic urticaria, localized heat urticaria, cold urticaria, aquagenic urticaria, and vibratory angioedema all require specific evaluation and treatment. Chronic idiopathic urticaria is usually controlled by antihistamines; depending on the circadian rhythm of the eruption, sedative or nonsedative antihistamines are prescribed. Some patients will require a combination of H_1 and H_2 antagonists, or even parenteral corticosteroids.

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Patients with urticaria and angioedema are commonly seen in medical practice, and those who render care should have knowledge of the types of urticaria and angioedema and their common causes and treatments.

Approximately 15% to 20% of the population experience one or more episodes of urticaria during their lifetime. The cutaneous appearance is easy to recognize, and many patients will have made their own diagnosis before presenting for treatment. Common urticarial lesions consist of pruritic erythematous papules, plaques, or wheals that vary from about a millimeter to several centimeters or larger in size. They may show central clearing, and their form may take on unusual serpiginous shapes. The lesions may be found on any part of the body. Individual cutaneous lesions are usually transient, lasting less than four hours. If particular lesions remain longer than 12 to 24 hours, the possibility of underlying vasculitis must be considered. Lesions of angioedema differ in that they are often not pruritic and consist of deeper dermal and subcutaneous swellings that most frequently involve the lips and eyelids. Angioedema often accompanies urticaria in its various forms but may occur by itself. Serious consequences may result if the edema involves such structures as the larynx. Lesions of urticaria and angioedema may be associated with systemic symptoms from direct visceral involvement or due to the release of circulating chemical mediators. These mechanisms may lead to diverse symptoms such as hoarseness, respiratory distress, abdominal pain, nausea, vomiting, diarrhea, arthralgias, headache, and hypotension. Even neurologic symptoms, such as seizures, have been associated with angioedema.

Histologically, urticarial wheals exhibit dermal edema with a sparse dermal perivascular lymphocytic infiltrate that may contain eosinophils. The predominant lymphocytes are activated $CD4^+$ T cells expressing DR surface markers. Under the electron microscope, degranulated mast cells and eosinophils are seen. Biopsy specimens of angioedematous areas show similar findings except that the edema and infiltration extend into the subcutis. A histologic study done on 43 patients with chronic urticaria revealed that their lesional skin contained ten times the normal number of mast cells and monocytes.[1] No explanation for the accumulation of these cells was apparent, but it has long been known that the mediators of urticaria are mast cell products.

The human dermis has between 7,000 and 12,000 mast cells per cubic millimeter. On toluidine blue-stained sections, these cells are identified by the presence of metachromatic oval granules, which may measure as much as 0.5 nm. Electron microscopy of these membrane-surrounded granules reveals a crystalline structure of scrolls, lattices, and gratings.

Several substances are known to induce the release of mediators from mast cells, including immunoglobulin (Ig) E, biologically active peptides (C3a, C5a, and lysosomal granule proteins), polymers (compound 48/80, dextran), enzymes (chymotrypsin, phosphatidases), and many other miscellaneous factors, including drugs and physical stimuli (Table 1). One human mast cell has about 300,000 binding sites for IgE. Dimerization of surface IgE through antigen bridging results in mast cell activation, including membrane lipid methylation, activation of adenylate cyclase, and the uncovering of a serine esterase activity. Granule-bound chemical mediator release is dependent on cyclic adenosine monophosphate (cAMP) and calcium. Activation of cutaneous mast cells results in the release of primary mediators of inflammation (preformed, granule-associated) and the release of secondary mediators of inflammation.

Although many mediators may play a role in the production of urticaria, histamine appears to be the primary mediator involved in most cases of acute urticaria. Injection of histamine will reproduce the symptoms and signs of urticaria, and administering antihistamines will relieve them. The cutaneous response to the intradermal administration of histamine is exemplified by the triple response of Lewis. Initially vasodilation begins in the area of injection, followed

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ABBREVIATIONS USED IN TEXT

cAMP = cyclic adenosine monophosphate
Ig = immunoglobulin

by a surrounding flare due to axon reflex. The transudation of fluid from the vessel to the extravascular compartment results in tissue edema, appreciated clinically as urticaria or angioedema. This histamine-mediated effect is attributed to the widening of the space between endothelial cells, allowing the passage of material from the intravascular to the extravascular compartments. Both eosinophils and polymorphonuclear leukocytes have positive chemokinetic movement in response to H_1 and H_2 agonists, but H_2-receptor effects appear to be inhibitory and H_1 stimulatory when assessing directed migration of each cell type to a preferred chemotactic factor.

The biologic effects of histamine follow its interaction with two specific classes of receptors on target cells, the so-called H_1 and H_2 receptors. A production of leaky venules attributed to a partial disconnection of endothelial cells is due to both H_1- and H_2-receptor effects.

Various leukocytes, including eosinophils and lymphocytes, have histamine receptors. Histamine through H_1 receptors appears to increase the expression of receptors for the C3b component of complement on human eosinophils. Suppressor T lymphocytes have H_2 receptors, and histamine appears to inhibit the development of a cytotoxic response.

Eosinophilic chemotactic factors of anaphylaxis consist of two closely related tetrapeptides that, when released by mast cells, result in the attraction of eosinophils and an increase in C3b receptors on eosinophil cell membranes. These factors are both chemotactic for eosinophils and deactivating for these cells once they have been attracted. Although these factors may have some chemoattractant effect on other granulocytes, these effects seem to be preferential for eosinophils. Eosinophilic chemotactic factors of anaphylaxis probably act by attracting eosinophils to a site, holding them there by deactivation, and then facilitating immune adherence and phagocytic functions.

Heparin is another granule-associated factor released by mast cells. The local effects of this substance include the stimulation of endothelial cell chemotaxis and proliferation, the augmentation of histaminase activity, and an inhibition of several steps of complement activation.

There are several chemical mediators released by the mast cell that do not exist preformed, as do the granule-associated factors, but are produced in response to mast cell stimulation. Platelet-activating factor(s) is produced in response to a stimulation of mast cells and results in the aggregation and release of serotonin from platelets. Several lipid factors are also produced by stimulated mast cells, including leukotrienes, which are more potent vasoactive substances than histamine.

Many other mediators—including kinins and kallikrein, acetylcholine, fibrinogens, and prostaglandins—may possibly cause or contribute to wheal formation in various situations. Intermediate-molecular-weight eosinophil chemotactic factors, which are released in a linear fashion with histamine, have been found. High-molecular-weight neutrophil chemotactic factor has been identified in the venous effluent of patients with cold urticaria. This substance deactivated neutrophils in a time- and dose-dependent manner.

Common Urticaria

For the purposes of this discussion, we will review the types of urticaria that are more commonly seen.

Urticaria is conveniently divided into acute and chronic types. Chronic urticaria refers to a frequently recurring urticaria over a period of greater than six weeks. Whereas the cause for acute urticaria is commonly ascertained, the inciting agent remains a mystery in more than 75% of cases of chronic urticaria (Table 2). Unlike chronic urticaria, acute urticaria is more likely to be mediated through an IgE mechanism. Furthermore, acute urticaria is usually found in young patients, as opposed to the chronic form that has been reported most frequently in middle-aged women.

Urticaria and angioedema may be produced by immunologic or nonimmunologic means. Immunologic mechanisms involve either type I (IgE-mediated, immediate hypersensitivity), type II (cytotoxic antibody-mediated), or type III (immune complex-mediated) reactions. Type II and type III events may lead to complement activation and the release of the anaphylatoxins, C3a and C5a, which provoke mast cell degranulation. These anaphylatoxins may also be more directly produced by the action of bacterial lipopolysaccharide on the alternative complement pathway. In addition, inflam-

TABLE 1.—*Nonimmunologic Histamine Releasers*

Polymers	Chemicals or Drugs
Dextran	Aspirin
Compound 48/80	Alcohol
Calcium ionophore A23187	Opiates
Bacterial toxins	Polymyxin B sulfate
Snake venoms	Colistin sulfate
Biologic polypeptides	Thiamine hydrochloride
Ascaris species	Tyramine
Jellyfish	Tubocurarine chloride
Portuguese man-of-war	Quinine sulfate
Spines and hairs of caterpillars	Radiographic dyes
Nettles	Scopolamine hydrochloride
Moths	Gallamine triethiodide
Foods	Dexamethonium
Shellfish	Stilbamidine isethionate
Strawberries	Chlortetracycline bisulfate
Egg white	Amphetamines
	Hydralazine hydrochloride
	Tolazoline hydrochloride
	Cinnamaldehyde
	Cinnamic acid
	Benzoic acid
	Sodium benzoate

TABLE 2.—*Causes of Urticaria*

Drugs	Physical agents
Foods	Dermatographia
Inhalants	Pressure
Infections	Cold
Insect bites	Cholinergic agents
Internal diseases	Solar light waves
Vasculitis	Heat
Mastocytosis	Water
Contactants	Vibration

matory responses to immune complexes may eventuate in the elaboration of other chemical mediators that promote vasodilation and plasma exudation, such as the kinins, prostaglandins, and leukotrienes, and contribute to the production of edematous wheal-like lesions.

Nonimmunologic mechanisms usually involve substances that directly incite the release of histamine and other mediators from mast cells. A list of such agents is given in Table 1. In addition, aspirin, which does not release histamine directly, has been shown to aggravate the eruptions in 20% to 40% of patients with chronic urticaria. Though aspirin may cause urticaria, its main effect is enhancement, an effect that may last as long as three weeks after ingestion. This mechanism is not well understood, but it is postulated that the action may be due to the ability of aspirin and other nonsteroidal anti-inflammatory drugs to inhibit prostaglandin synthesis.

Prostaglandins of the E series interact with mast cells to elicit increases in cAMP levels, which decreases mediator release. A decrease in prostaglandin E production may enhance release and may also cause more arachidonic acid to be metabolized through the lipoxygenase pathway, which is unaffected by aspirin. This second pathway leads to leukotriene compounds with potent vasodilatory, exudative, and bronchospastic effects of their own. In addition, salicylates have been shown to inhibit a step in one pathway of histamine catabolism. Aspirin-sensitive patients have an increased incidence of urticarial reactions to azo dyes and benzoic acid, which are frequent food additives, and to nonsteroidal anti-inflammatory drugs.

Drugs taken parenterally or orally are among the most common causes of urticaria. Also, urticarial reactions make up a substantial percentage (23%) of all cutaneous drug reactions. Nearly any drug may be an inciting agent, and immunologic (types I and III) or nonimmunologic mechanisms may be responsible. Common offenders include penicillin, cephalosporins, aminoglycosides, sulfonamides, serum, dextran, polypeptide hormones, barbiturates, hydralazine, phenylbutazone, tranquilizers, hydantoins, quinine, and mercurial diuretics.

Most drugs and simple chemicals are of low molecular weight and are unable to stimulate the immune system unless they react irreversibly with proteins to form multivalent drug-protein complexes. Drugs such as penicillin that are easily able to react with proteins are immunogenic.

Penicillin is the most common urticaria-producing drug on an allergic basis. The average incidence of IgE-mediated penicillin allergy is about 2%, and life-threatening complications occur in 2% to 13% of these. Reactions may be divided by the time of onset after administration into immediate (15 to 20 minutes), accelerated (30 minutes to 48 hours), and delayed (after 2 days). Extremely small amounts of the drug may elicit hypersensitivity phenomena in sensitive persons. Coleman and Swineford reported the case of a patient in whom an intradermal injection of only 5 μU precipitated a systemic reaction.[2] There is also a report of a case of urticarial eruption in a woman who presumably absorbed penicillin through her vaginal mucosa from the semen of her sexual partner who was taking penicillin. It is particularly important to remember that traces of penicillin are frequently found in milk and other dairy products.

In patients with a history of "penicillin reaction," previous skin testing may effectively screen for IgE-mediated sensitivity. Skin testing is carried out using the major determinant, which represents 95% of metabolized penicillin (penicilloyl-polylysine [Pre-Pen]) and the minor determinant mix (not generally available) or a dilute solution of penicillin G (10,000 U per ml). The minor determinants are more frequently associated with anaphylaxis than the major determinants, so it is important to use either the minor determinant mix or dilute penicillin G in addition to penicilloyl-polylysine. Scratch tests should be applied before intradermal testing to avoid serious reactions. Test sites are examined for wheals after 15 to 20 minutes; if positive, the use of β-lactam antibiotics should be avoided (penicillin, semisynthetic penicillins, and cephalosporins). In certain life-threatening infections, however, these antibiotics are required. Sullivan and associates detailed a successful oral desensitization regimen used for patients with endocarditis, *Pseudomonas* species sepsis or pneumonia, or staphylococcal infections that required the use of penicillin or semisynthetic penicillins.[3] Parenteral desensitization techniques have also been used, but Sullivan and colleagues point out that some cases of anaphylaxis and more cases of urticaria have resulted from parenteral desensitization.

Food and food additives are probably too frequently implicated in urticaria. Common urticariogenic foods include shellfish, fish, eggs, nuts, chocolate, berries, tomatoes, cheese, and milk. In a recent study only 1.9% of the reactions had a food-linked origin.[4] Frequent food additives or contaminants include azo dyes, benzoic acid, penicillin, yeasts, citric acid, and salicylates. Some of these act nonimmunologically and some act through IgE hypersensitivity. Tyramine, a phenolic amine, is found in foods such as lobster and scallops and in foods changed by bacteria, molds, or yeasts. It induces histamine release nonimmunologically and is also catabolized by one of the enzymes that catabolizes histamine and may compete with histamine for degradation. This substance may be responsible for the urticariogenic effect of these foods, bacteria, and fungi.

Inhalant allergens, including pollens, spores, animal danders, and dust inhalants, have been rarely reported to produce urticaria. This route of exposure may be a significant problem, however, as evidenced by Tannenbaum's patient in whom, following exposure to a wide variety of substances, severe angioedema developed, making it impossible for her to leave her house.[5]

Infections of many diverse types have been associated with urticaria. Some commonly associated viral infections include hepatitis B (often with preicteric symptoms of serum sickness) and mononucleosis. Immune complex mechanisms have been shown to be important in these diseases. Dermatophyte and candidal infections can also be urticariogenic. Some dermatophyte antigens may cross-react with airborne molds *(Alternaria* and *Cladosporium)*, and, therefore, skin tests for immediate reaction to *Trichophyton* species may be positive in persons allergic to molds. Parasitic infections are frequently searched for but rarely found in patients with recurrent urticaria. There have been reports of urticarial eruptions with giardiasis, amebiasis, trichomoniasis, malaria, and scabies. Localized bacterial infections, such as sinusitis, dental apical infections, and gastrointestinal tract infections, may, on occasion, elicit urticarial eruptions.

Insect-bite hypersensitivity, particularly hymenoptera

sensitivity, can be an important allergic cause of urticaria, angioedema, and anaphylaxis. The hymenoptera are divided into two families, the Apidae (honeybees and bumblebees) and the Vespidae. The Vespidae are further divided into the genera *Polistes* (wasps) and *Vespula* (hornets and yellow jackets). Many patients are sensitive to the venom of insects from both families, as diagnosed by skin tests.

Many varieties of internal diseases are associated with urticaria. Hormonal disturbances have occasionally been implicated, particularly thyroid autoimmunity.[6] A few cases of progesterone hypersensitivity have also been reported. In these cases, exacerbations occurred monthly, seven to nine days before the menses, the times of peak progesterone levels. Urticaria and angioedema have also been reported in rheumatic fever, rheumatoid arthritis, lymphoreticular malignancy, and carcinoma. Of the collagen vascular diseases, systemic lupus erythematosus is most commonly associated with urticaria, as it is found in 6.9% to 13% of cases.[7,8] In lupus, the wheals are often produced by type III immune complex mechanisms, and eruptions often occur concurrently with fever, decreased complement levels, increased erythrocyte sedimentation rate, and increased disease activity. A lesional biopsy usually reveals vasculitis.

Immunofluorescence studies have shown deposition of the major basic protein of eosinophils in lesions from patients with chronic idiopathic urticaria, episodic angioedema, and facial edema. Major basic protein causes a release of histamine from human basophils and induces wheal-and-flare reactions on intradermal injection.[9] Neutrophilic urticaria is characterized by a neutrophilic venulitis without fibrinoid necrosis, hemorrhage, or leukocytoclasia. Results of laboratory studies are normal. Patients respond to antihistaminic agents. The histologic features and the therapeutic course of these patients are compatible with a phase or type of chronic urticaria.[10]

Urticarial Vasculitis

Urticarial vasculitis is an interesting disorder first brought to light by McDuffie and co-workers, who reported on four patients with urticarial-appearing eruptions that showed necrotizing vasculitis on biopsy.[11] The authors attributed the findings to an immune complex syndrome.

Clinically the lesions appear similar to common urticarial wheals, except that the individual lesions remain for longer than 24 to 72 hours. They may show petechiae or purpura, particularly as they resolve. Residual pigmentary changes and scaling may be noted. The lesions may be pruritic or painful, and patients may have angioedema.

Associated symptoms are most often rheumatologic—arthralgias and arthritis—in cases reported, but a wide spectrum of disease severity has been noted from mere cutaneous eruptions to severe systemic involvement. A substantial percentage of patients have shown hypocomplementemia, and there is evidence for activation of both the classical and alternative complement pathways. The erythrocyte sedimentation rate is the laboratory test most frequently giving abnormal results, and it is elevated in most patients. This test may be the most useful screening device for vasculitis in urticaria.

Histologically, vasculitis shows endothelial swelling with fibrin deposition. Vessels may be occluded. The cellular infiltrate usually shows a predominance of polymorphonuclear leukocytes with nuclear fragmentation (leukocytoclasia). Immunoglobulin and complement deposits are found in early lesions. In view of the many mediators of inflammation that produce vasodilation and exudation and the anaphylatoxin effects of complement components C5a and C3a, it is not surprising that this type of lesion could exhibit urticarial features clinically.

The possibility of underlying vasculitis should be considered in patients with chronic urticaria. Some researchers have estimated the percentage of underlying vasculitic causes to be at 20%, but others found vasculitis in biopsy specimens of only 1 of 43 patients with chronic urticaria.[1,12] Corticosteroids, salicylates, and immunosuppressive agents in various combinations have been used to treat urticarial vasculitis. Indomethacin has been used successfully. Nevertheless, some authors think that no treatment has been particularly effective. Besides this group of patients with urticarial vasculitis of unknown cause, patients can be seen, as previously mentioned, with vasculitis in urticarial lesions associated with preicteric hepatitis B, serum sickness, collagen vascular diseases, mononucleosis, and in selective C1q deficiency. Hepatitis B is an important consideration if a patient presents acutely with serum sickness-like symptoms of urticaria, arthralgias, proteinuria, hematuria, and, sometimes, angioedema.

Contact Urticaria

Contact urticaria consists of a wheal-and-flare response to substances applied to intact skin. The reaction usually occurs within 20 to 30 minutes. Once again, the mechanism may be immunologic, nonimmunologic, or unclassifiable, but allergic types generally involve a type I mechanism. Both types are best diagnosed by open patch tests observed for 30 minutes for allergic and for 45 minutes for nonallergic urticarial reactions. Table 3 lists implicated allergic contact urticariogens. Maibach and Johnson divided allergic contact urticaria into four stages[13]: stage 1 shows local urticaria; stage 2 is when there is urticaria plus angioedema; stage 3 involves urticaria plus asthma, rhinoconjunctivitis, and gastrointestinal or orolaryngeal dysfunction, which has rarely been pro-

TABLE 3.—*Causes of Allergic Contact Urticaria*

Acrylic monomer	Hair sprays
Aminothiazole	Horse serum
Ammonia	Lindane
Animal dander	Monoamylamine
Arthropods	Nail polish
Benzophenone	Penicillin
Benzoyl peroxide	Perfumes
Carrots	Phenylmercuric propionate
Castor beans	Platinum salts
Cat saliva	Potatoes
Cephalosporins	Silk
Cetyl alcohol	Sodium sulfide
Chlorpromazine	Spices
Cobalt chloride	Stearyl alcohol
Cod liver oil	Streptomycin
Diethyltoluamide	Sulfur dioxide
Dog saliva	Taliphatic polyamide
Estrogenic creams	Tetanus antitoxin
Exotic woods	Wheat
Flour	Wool
Formaldehyde	

duced by patch testing; and stage 4 refers to urticaria plus anaphylaxis. These reactions have reportedly been caused by substances such as penicillin, mechlorethamine, epoxy resin, neomycin, chloramphenicol, amino phenazone, bacitracin, and the ubiquitous balsam of Peru (found in cosmetics, soaps, deodorants, and perfumes). The mechanism (or mechanisms) by which balsam of Peru causes contact urticaria is controversial. As opposed to the allergic and unspecified types, nonimmunologic contact vasoactive mediator release is rarely a serious problem but may be more common. Offenders include benzoic acid, dimethyl sulfoxide, cinnamaldehyde, balsam of Peru, benzocaine, sorbic acid, ethyl alcohol, butyric acid, sodium benzoate, and acetic acid. Keeping cinnamaldehyde in mind is useful because many mouthwashes and toothpastes contain this compound; it may, therefore, be a cause of lip and oral mucosal swelling. Ammonium persulfate is an urticariogen that acts by an unknown mechanism. Though urticaria from contacts is uncommon, the possibility should be borne in mind when a patient presents acutely without any internally administered identifiable cause.

Mastocytosis

Mastocytosis denotes the presence of increased numbers of mast cells in a variety of organs. Skin involvement alone is most frequent and often is asymptomatic. The other organs that can be involved include bone, gastrointestinal tract, liver, lymph nodes, and spleen. There is no sex predominance, and heredity does not appear to be a factor. Mastocytosis usually presents in infants and small children, most showing signs by age 2. It occurs less commonly in adults, although they are more likely to have systemic involvement. Symptoms are produced by degranulation of the overabundant mast cells leading to local or systemic symptoms due to circulating mast cell mediators, particularly histamine.

Cutaneous mastocytosis is referred to also as urticaria pigmentosa. The most common appearance is of red-brown macules and papules over the trunk and extremities. A peculiar adult form, telangiectasia macularis eruptiva perstans, shows diffuse pigmented, telangiectatic macules. A rare erythrodermic form also has been noted. Solitary mastocytomas occur at birth or in early infancy. Stroking lesions of urticaria pigmentosa will produce whealing (Darier's sign), and patients may have a considerable problem with dermatographism. Flushing or pruritus may be triggered by temperature changes, exercise, hot baths, stress, stroking, or drugs (particularly nonimmunologic histamine releasers). Histologically, all types show mast cells infiltrating the upper third of the dermis or scattered in tumorlike dense aggregates.

Systemic mastocytosis is seen in approximately 10% of all patients with mastocytosis, and there is occasionally an absence of skin lesions. The skeletal system and the gastrointestinal tract are the most common sites. Symptoms of attacks include intense pruritus, headache, diarrhea, bronchospasm, rhinorrhea, flushing, hypotension, nausea, vomiting, tachycardia, dyspnea, and syncope, and the condition may sometimes resemble the carcinoid syndrome. Rarely, hemorrhagic episodes may be associated with mast cell heparin release. Elevations of urinary histamine, its metabolite, 1-methyl-4-imidazoleacetic acid, or serum histamine may aid in the diagnosis. Abnormalities of these values may be found in either cutaneous or systemic disease, although urinary histamine cannot always be relied on to relate to disease activity.

Treatment in mild cases requires only H_1-blocking antihistamines. The addition of the H_2 blocker, cimetidine, has given some patients increased relief from cutaneous and gastrointestinal symptoms and appears to be preferable to using either alone.

Cromolyn sodium has proved to be an effective treatment for systemic mastocytosis in a double-blind study and for cutaneous mastocytosis in a single-blind trial.[14,15] Its mechanism of action is unknown, but an inhibition of mast cell degranulation has been postulated.

Another therapeutic modality involves an inhibition of prostaglandin biosynthesis. Mast cells release a quantity of prostaglandin D_2. Roberts and associates correlated elevated urinary levels of a prostaglandin D_2 metabolite with flushing, hypotension, and tachycardia in two patients.[16] In one patient with uncontrolled life-threatening attacks, the addition of aspirin to his antihistamine regimen alleviated his symptoms almost entirely. There is danger, however, in the use of aspirin or other nonsteroidal anti-inflammatory agents, as idiosyncratic exacerbations have occurred. Theoretically, blocking the biochemical pathway leading to the prostaglandins may divert more arachidonic acid into the formation of leukotrienes, which are potent vasodilatory and bronchospastic agents.

A final treatment modality in cutaneous disease that combines photosensitizers (psoralens) with long-wave ultraviolet light has been beneficial to some. Granerus and colleagues correlated decreased symptoms with a decrease in the major urinary metabolite of histamine after using this therapy.[17]

Physical Urticarias

Urticaria and angioedema may be induced by physical agents, such as stroking, pressure, cold, light, heat, water, and vibration. Some of these stimulants act through IgE-mediated mechanisms, as shown by the Prausnitz-Küstner (passive transfer) reaction. Physically provoked reactions may be responsible for 7% to 17% of cases of chronic urticaria.[18] Though they are not usually the cause of significant morbidity or mortality, they occasionally can be, and health care providers should be aware of their existence.

Dermatographism

It is important to recognize dermatographism, a common form of urticaria, because it may be mistaken for common urticaria. Although some degree of reaction to stroking the skin is found in about half the population, the rapid appearance of a wheal at the site of firmly stroked skin is found in 1.5% to 4.24% of normal persons.[19] The wheal usually fades within 30 minutes. This immediate response can be IgE-mediated, with demonstrably positive passive transfer tests. Occasionally the response is frequent and severe enough to be symptomatic. Dermatographism is common enough to coexist with other forms of urticaria. Patients with more severe forms of the disorder, who have exquisite sensitivity to pressure on the skin, may present with a more typical urticarial appearance, and the clue to the contrary is the predisposition for lesions to appear where clothing rubs the skin. Patients with mastocytosis or the hypereosinophilic syndrome are predisposed to dermatographism. They usu-

ally have a notable decrease in symptoms with the use of antihistamines, such as hydroxyzine hydrochloride, cyproheptadine hydrochloride, or diphenhydramine hydrochloride. Giving aspirin, indomethacin, or cimetidine has not been beneficial.

A much less common type of dermatographism has a delayed onset, occurring 1 to 8 hours after the stimulus, and is often a tender, deeper swelling that lasts 24 to 48 hours. The mechanism is unknown, and passive transfer has not been accomplished. This disorder may occasionally be difficult to distinguish from delayed pressure urticaria.

Pressure Urticaria or Angioedema

Pressure urticaria or angioedema may occur immediately, or a delayed type may occur four to six hours after pressure is applied. The lesions may last as long as 48 hours, and they have a refractory period of 24 to 48 hours. The deep swellings are often tender and may be associated with malaise and a viral-like syndrome of aches. Frequent sites are under straps, belts, or on the palms and soles.

The common activities that induce delayed pressure urticaria are standing, working, or sitting on a hard surface, using a screwdriver or hammer, hand clapping, carrying a handbag, wearing tight-fitting clothing, dental work, kissing, sexual intercourse, and tampon usage. Delayed pressure urticaria is slightly more common in men. Antithyroid microsomal antibodies are found in 30% of patients. The lesions are morphologically similar to classic late-phase cutaneous reaction. In patients who had skin tests positive to food allergens, none lost their delayed pressure reactivity while on a diet omitting the food allergens to which they gave positive reactions. This disease cannot be cured by eliminating the "offending agents" from the diet. The diagnosis of delayed pressure urticaria can be easily made by dermographometric testing. Delayed dermatographism may be the same disorder as delayed pressure urticaria induced by a different method of pressure application. Parenteral corticosteroid therapy remains the only known effective treatment for disabling delayed pressure urticaria, knowing that too often the high doses required will induce unacceptable side effects.[20-22]

Cold Urticaria

Cold urticaria has the potential of being a life-threatening disease, making it important to recognize. In this usually acquired type of urticaria, patients with exposure to a decrease in ambient temperature will have hives develop at the time of cooling or on rewarming. Extreme and even fatal reactions have occurred when affected persons emerge from swimming in cold water.

Acquired cold urticaria is the most common form seen. This disease results in whealing of the skin after exposure to cold contact or cold immersion. This usually occurs minutes after rewarming, and the wheals last from one to two hours. In some persons, the mucous membranes are affected, and cold stimulation can result in a swollen tongue.

A few patients with cold urticaria have associated cryoproteins, such as cryoglobulins, cryofibrinogens, cold hemolysins, and possibly cold agglutinins. These are factors that should be sought in the workup of a new patient with cold urticaria. They are thought to induce urticaria by inducing the complement factors C3a and C5a. Some patients with acquired cold urticaria do not have a cryoprotein but do have an associated circulating immune globulin. Passive transfer has been shown for some subjects. The serum factor most often appears to be IgE, although IgM and IgG have also been implicated.

The usual test for cold urticaria is a three- to five-minute application of an ice cube to forearm skin. During the rewarming phase, a wheal occurs that conforms to the area cooled.

Leukotriene E_4 and histamine levels, when measured in the blood draining the site of a cold challenge in patients with clinical histories of cold urticaria, were increased after a typical clinical response to the challenge. No increase in leukotriene E_4 or histamine levels was observed following a cold challenge in nonresponding persons.[23]

Cyproheptadine hydrochloride is the standard antihistamine used for symptomatic relief. Acquired cold urticaria lasts months to years, and patients must be cautious about cold exposure.

Familial cold urticaria is a rare, usually autosomal dominant condition that is associated with burning wheals appearing 30 minutes to 3 hours after exposure to a cold wind. The urticaria usually lasts for 48 hours. It is characteristically accompanied by fever and leukocytosis and sometimes arthralgias and headache. The mechanism of this disease is unknown.

Cholinergic Urticaria

Cholinergic urticaria is the second most common after dermatographism. The pruritic lesions are distinctive, consisting of tiny 2- to 3-mm wheals with surrounding flares. These wheals develop in response to exercise or warm temperatures, which, in some cases, may be associated with angioedema, bronchospasm, and anaphylaxis. Symptoms indicative of cholinergic stimulation may also occur. Elevated plasma histamine levels, which peaked at 20 to 25 minutes, have been found in some patients. Soter and co-workers found an increased release of histamine, as well as chemotactic factors for eosinophils and neutrophils.[24] The cutaneous response may be mediated by cholinergic sympathetic nerve fibers and may indirectly lead to mast cell degranulation. Confirmatory intradermal skin testing may be attempted using acetyl-β-methylcholine or nicotinic acid tartrate, but these tests are positive in only about a third of the patients with the disease, and the results are not always reproducible. Commens and associates emphasized that provocation by exercise or a hot bath is much more effective than skin tests.[25] It is notable, however, that Sheffer and colleagues have possibly distinguished a new syndrome of exercise-induced anaphylaxis that occurs with angioedema and urticaria and in which there are sizable increases in serum histamine levels.[26] Others have shown similar cases that occurred only in a strict time relation to meals.

Antihistamines, particularly hydroxyzine hydrochloride, are relied on for the treatment of cholinergic urticaria; however, because refractory periods of as long as 24 hours can sometimes be induced by a reaction to a hot bath or exercise, daily exercise has been used as a method of preventing attacks.

Solar Urticaria

Solar urticaria occurs within minutes after exposure to light of various wave lengths and fades 15 minutes to 3 hours after it begins. This abnormal response to light has occasionally been seen in cases of systemic lupus erythematosus,

porphyria cutanea tarda, erythropoietic protoporphyria, and polymorphous light eruption. Monochromatic phototesting, including the use of a new instrument called a "spectrodermograph," has allowed classification of this disease by eliciting the wave length. Most commonly, patients react to wave lengths in the sunburn range—290 to 320 nm. Positive passive transfer has been found in this group and in those who react in the range of 400 to 500 nm. Some have postulated that antibody may react with a photoproduct, leading to mast cell degranulation. Because Soter and co-workers found increased histamine and chemotactic factors for neutrophils and eosinophils in venous blood after light challenge,[24] it is not surprising that a few patients may experience wheezing, dizziness, and headache after lengthy exposures.

Treatment should involve avoiding the harmful light wave lengths. Antihistamines may be useful; β-carotene is useful in some patients but does not protect against long wave or visible light. The development of tolerance to light may occur with repeated exposures. Psoralens plus ultraviolet light (PUVA) therapy has been found useful by some. Ravits and colleagues recommend the use of combinations of induced pigmentation, oral β-carotene, and antihistamines.[27]

Localized Heat Urticaria

In localized heat urticaria, a rare form of physical urticaria, localized, pruritic wheals occur within minutes of heat contact and may last as long as an hour. Provocative testing is done with a metal tube filled with hot water. Passive transfer attempts have been unsuccessful. Histamine and other mast cell mediators may be involved in the response, but the mechanism remains unknown. Studies by Tóth-Kása and associates suggest that chemosensitive nerve endings may be needed to allow the response.[28] Some authors have reported finding complement abnormalities in one patient that were indicative of alternative pathway activation.[29] Treatment with antihistamines has been helpful to some patients but not to others.

Aquagenic Urticaria

Patients with aquagenic urticaria, an uncommon type, experience the formation of pruritic wheals that are often follicular in skin areas that have come in contact with water. Clinically, the morphology may be difficult to distinguish from that of cholinergic urticaria. The length of contact needed to produce lesions has varied from minutes to half an hour. Other solvents, such as ethanol or acetone, do not induce aquagenic urticaria. The mechanism may involve acetylcholine, as topical scopolamine abolished the wheal production.[30] In addition, histamine levels were increased in venous drainage from the stimulation site.

Antihistamine treatment may give partial control, but the benefit has been inconsistent; cyproheptadine and promethazine hydrochloride were more efficacious than chlorpheniramine maleate and hydroxyzine hydrochloride.

Vibratory Angioedema

Vibratory angioedema was first described by Patterson and co-workers in a family in whose members localized swelling developed after five minutes of contact with a vibratory stimulus.[31] The swellings lasted hours to days and were sometimes associated with headache. The inheritance pattern suggested autosomal dominant transmission. Sporadic

TABLE 4.—*Commonly Used Antihistamines (H_1 Blockers)*

'Classical' Antihistamines	*'New Generation' Antihistamines*
Alkylamines	
Chlorpheniramine maleate*	Acrivastine†‡
Dexchlorpheniramine maleate (Polaramine)	
Brompheniramine maleate (Dimetane)	
Tripolidine hydrochloride (Actidil)	
Ethanolamines	
Diphenhydramine hydrochloride*	Ketotifen fumarate (Zaditen)‡
Dimenhydrinate*	Oxatomide (Tinset)‡
Clemastine fumarate*	
Cinarrizine (Midronal)‡	
Ethylenediamines	
Tripellenamine (Pyribenzamine) citrate, hydrochloride	
Piperazines	
Hydroxyzine hydrochloride,* pamoate*	Cetirizine hydrochloride (Zyrtec)†‡§
Meclizine hydrochloride*	
Phenothiazines	
Promethazine hydrochloride*	Mequitazine (Primalan)†‡§
Piperidines	
Cyproheptadine hydrochloride (Periactin)	Loratadine (Claritin)†§
Azatadine maleate (Optimine)	Astemizole (Hismanal)†§
	Terfenadine (Seldane)†
	Azelastine hydrochloride‡
Tricyclics	
Doxepin hydrochloride*	
Amitriptyline hydrochloride*	
Imipramine hydrochloride*	
Desipramine hydrochloride*	

*Several manufacturers produce this drug.
†Nonsedative.
‡Not available in the United States (April 1989).
§Once-a-day dosage.

cases have also been reported. Using a laboratory vortex as a method of stimulation, Kaplan and Beaven demonstrated elevated venous histamine levels from the area, stimulated within a minute of the application of vibration.[32] Complement levels in these patients are normal, and passive transfer has not been accomplished. No therapy other than the avoidance of vibration has been useful.

Treatment

In all cases of urticaria, a search for the inciting agent must be made, but as mentioned above, in patients with chronic urticaria, this is frequently fruitless. Elimination and readdition diets may be helpful. Patients found to be sensitive to salicylates, tartrazine, or benzoates should attempt to eliminate these items. This may be difficult or impossible, however, as these are not only additives but occur naturally as well. In 1981 a review listed drugs that contain tartrazine.[33]

Nonphysical urticarias may also be aggravated by external vasodilatory influences, such as heat, exercise, sunburn, vasodilating drugs, fever, stress, and alcohol. If possible, these should be avoided.

In general, H_1-blocking antihistamines are the mainstay of therapy for acute and chronic urticaria. Their antagonism of histamine is competitive and reversible. These compounds are readily absorbed in the gastrointestinal tract.

The antihistamines are categorized by chemical type, though the basic substituted ethylamine structure, present also in histamine, is common to most (Table 4).

Two broad groups of antihistamines can be used to treat chronic urticaria: "classical," sedative ones, often available over-the-counter, and new, nonsedative, available by prescription only, and expensive. Most classical antihistamines act rapidly, will control cholinergic urticaria owing to their anticholinergic and antiserotonin activities but can be responsible for long-lasting somnolence, and their use is incompatible with everyday activities. Most nonsedative antihistamines, such as terfenadine, astemizole, loratadine, and cetirizine hydrochloride, are slower acting than classical or traditional antihistamines, but some, such as astemizole, can protect a patient for a number of days, thereby reducing the total cost of the treatment.[34-37]

Some patients respond to the use of classical antihistamines with central nervous system stimulation at conventional doses and complain of restlessness and insomnia; this is mostly the case at both ends of the lifespan—that is, infants and toddlers, and elderly patients. Rarely, small doses may evoke epileptic seizures in patients with focal central nervous system lesions. Antihistamines themselves rarely evoke systemic allergic reactions. It is important to remember that ethylenediamine and diphenhydramine are potent contact sensitizers (delayed type IV hypersensitivity). If a patient is sensitized to one of these, ingestion could lead to widespread drug eruption or cause a previously quiescent dermatitis to flare. The ethylenediamine antihistamines, as well as hydroxyzine, can cross-react with ethylenediamine. Aminophylline preparations also contain this compound. If a patient does not respond to the use of one antihistamine, it is best to choose another that is in a different chemical category. Increasing the dose will only produce side effects. Combining two antihistamines is not recommended.

Among the most potent, and probably the most useful, antihistamines for treating chronic urticaria are the tricyclic antidepressants, doxepin hydrochloride, amitriptyline hydrochloride, and imipramine hydrochloride.[38,39] Their side effects, however, should be seriously considered: anticholinergic effects with blurred vision, urine retention, dryness of the mouth, and the like. Any underlying psychiatric disease warrants the opinion of a specialist. Shertzer and Lookingbill recommended using hypnosis and relaxation therapy in patients with chronic urticaria[40]; compared with baseline and control session values, a hypnosis session provided relief of pruritus, but there was no change in the number of hives. At a follow-up examination of 15 patients a year after the completion of experimental sessions, 6 were free of hives and another 7 reported improvement.[40]

Because human skin blood vessels contain H_2 as well as H_1 receptors and an H_2 agonist can lead to wheal formation, there is a good rationale for using the H_2 blocker, cimetidine, as an adjunct in treating chronic urticaria. Combination therapy using both H_1 and H_2 blocking agents has met with varying success.[41] Cimetidine should not be used alone, however, and H_2 blockade may negate the feedback inhibition of histamine itself on mast cell degranulation, which is mediated through the H_2 receptor.

Ortolani and associates showed some benefit during challenge tests of cromolyn sodium in patients with chronic urticaria who were sensitive to aspirin and tartrazine.[42] Inhibitors of mast cell degranulation (terbutaline sulfate, ketotifen fumarate), used in conjunction, led to improvement in ten patients with chronic urticaria. Epinephrine is transiently helpful, especially in patients with severe bouts of acute urticaria. Not only does this drug help to decrease cutaneous vasodilation, but it also inhibits mast cell degranulation by raising cAMP levels.

Topical corticosteroids are not efficacious in urticaria, but parenteral corticosteroids have been used. The rationale for their use is not clear in histamine-mediated urticaria, but when other mediators are implicated, their use may be plausible. Corticosteroids do inhibit the release of arachidonic acid from cellular phospholipids, thus inhibiting the conversion of arachidonic acid into both prostaglandins and leukotrienes. Furthermore, in types of urticaria mediated by type III immune complex reactions or other mechanisms involving complement activation, parenteral steroids may be useful. Stanozolol appears to act synergistically with glucocorticosteroids, and used together they may be capable of inducing remission in some patients, requiring the use of parenteral steroids to control angioedema.[43]

In summary, urticaria and angioedema are cutaneous and subcutaneous reaction patterns that may be precipitated by a host of mechanisms. In addition, lesions that may be identical in clinical appearance to the types described above may be seen in patients with other diseases as varied as bullous pemphigoid, erythema multiforme, rashes of pregnancy—prurigo gestationis of Besnier, pruritic urticarial papules, and plaques of pregnancy—and the gyrate erythemas. A multitude of chemical mediators, many probably yet undiscovered, may be important factors in evoking cutaneous responses such as these.

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Medical Staff Conference

Physician Payment Reform—An Idea Whose Time Has Come

Discussant
PHILIP R. LEE, MD

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Homer A. Boushey, MD, Professor of Medicine, and Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD*: *For this conference Dr Philip R. Lee will speak on physician payment reform. He is uniquely qualified to speak on this subject. By way of background, Dr Lee is a professor of social medicine and has served as director of the Institute for Health Policy Studies at the University of California, San Francisco, since 1972. He was chancellor at this institution from 1969 to 1972 and was Assistant Secretary for Health and Scientific Affairs in the US Department of Health, Education, and Welfare from 1965 to 1969. He is the author of over 100 articles in the health field and has coauthored numerous books, including* Pills, Profits, and Politics; Primary Care in a Specialized World; The Nation's Health; Exercise and Health; Pills and the Public Purse; Prescriptions for Death: The Drugging of the Third World, *and, most recently,* Drugs and the Elderly: Clinical, Social, and Policy Perspectives. *His teaching and research endeavors in the field of health policy have focused on physician payment, prescription drugs, reproductive health policy, and policies and costs related to the acquired immunodeficiency syndrome. He has been a frequent adviser to federal, state, and local health policymakers and serves on numerous advisory boards and planning groups. Until January 1989 he served the city and county of San Francisco as president of the Health Commission, and since July 1986 he has served as chair of the Physician Payment Review Commission established by the US Congress.*

PHILIP R. LEE, MD†: 1989 may well be remembered as the year of physician payment reform. The Physician Payment Review Commission submitted its recommendations to Congress in April. In December Congress enacted the Omnibus Budget Reconciliation Act of 1989, adding a new section on payment for physicians' services. This section provides for a comprehensive package of Medicare physician payment reforms that includes the establishment of a resource-based relative value fee schedule, limits on balance billing by physicians, and performance standard rates of increase for expenditures and volume of physicians' services.

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Fee-for-Service Payment—A Long-Standing Practice

Public policy deliberations over physicians' fees are not new. In the United States, fee for service has been the dominant method used to pay physicians.[1] The initial act of the nation's first state medical society (New Jersey) was to establish a fee schedule for physicians.[2] One of the first acts of the Boston Medical Society was to establish a fee schedule.[3] A prominent member of that society, Dr Bowditch, refused to accept the fee schedule as payment in full, establishing what was to be a long tradition of balance billing by physicians.

Until the establishment of private health insurance in the 20th century, most physicians were paid directly by their patients. In billing, physicians often followed fee schedules established by state or local medical societies. As health insurance coverage grew rapidly and began to include physicians' services in the 1950s, a major change occurred in physician payment with the California Medical Association's pioneering role in the development of a relative value scale. This was the first attempt to make explicit judgments with respect to the value of one service versus another. The next major development occurred in 1965 with the enactment of Medicare.

When Medicare was enacted in 1965, Congress established policies for physician payment that were designed to assure physician participation in a program that they had strongly opposed. To set payment levels for physicians' services, Medicare adopted the usual, customary, and reasonable fee screen system, which was called the customary, prevailing, and reasonable (CPR) fee screen system by Medicare.[4] Generally, the reasonable charge—recently called the "approved" charge by the Health Care Financing Administration (HCFA)—is the smallest of the actual charge for the service by physicians, the physician's customary charge (the median charge for that service by the physician in the past), or the prevailing charge (the charge for the same or similar services by physicians in the locality). The prevailing charge has been set by HCFA at a level no higher than is necessary to cover the 75th percentile of physicians' customary charges for the service in the locality.[5,6] Fee screens are also used by

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ABBREVIATIONS USED IN TEXT

CPR = customary, prevailing, and reasonable [fee screen system]
HCFA = Health Care Financing Administration

many major health insurance plans, but they are less structured and less stringent than under the CPR system.[7]

Before the Medicare program was implemented on July 1, 1966, it was feared that even with this new program, the elderly might have limited access to health care. This concern proved to be groundless as physicians proved willing to participate, despite their bitter opposition to the enactment of the program. The CPR payment system, whatever its other faults, did assure the elderly access to physicians' services. The past 23 years' experience with the CPR system has confirmed the early response of the medical profession. Whatever difficulties have emerged with the CPR method of payment, physicians have shown a willingness to care for Medicare beneficiaries.

The Physician Payment Review Commission recently completed a survey of beneficiaries and found that less than 1% of Medicare beneficiaries felt that they were denied access to care for financial reasons. Only 7% had difficulty obtaining care for financial reasons.[8] Considering that a substantial number of elderly have incomes below the poverty line, this is an important achievement.

Problems Associated With the CPR Payment Policy

If access is not a problem, what is? Since the enactment of Medicare and the adoption of the customary, prevailing, and reasonable method of payment, health care costs have risen steadily and rapidly. Also, a system of pricing has evolved that has resulted in wide payment differentials among types of procedures, localities, specialties, and sites of care that cannot be explained by differences in physicians' practice costs. Over the years, a number of problems associated with the CPR method of physician payment have been identified.[4,6,7,9–15] Following are some of the problems identified by the Physician Payment Review Commission:

- It encourages fee inflation;
- Continued rising health care costs and expenditures have increased the taxpayers' burden and eroded the financial protection of beneficiaries;
- It creates distortions in relative payments for physicians' services and among geographic areas;
- The payments are not predictable;
- It encourages the adoption and widespread use of new or additional technologies and services; and
- The administration of the program is complex, time-consuming, and costly.

Increases in Medicare Part B Expenditures

Congress is particularly concerned about Medicare costs and has focused increasingly on how these expenditures might be contained. Medicare Part B expenditures (non-hospital payments) have been rising rapidly since Medicare was implemented. Between 1967 and 1988, Part B outlays increased from $799 million to $34.9 billion, more than a 40-fold increase. During this same period, hospital expenditures (Part A) increased only half as rapidly, from $2.6 billion to $52.7 billion, a 20-fold increase (Table 1).[16]

TABLE 1.—*Medicare Outlays, Fiscal Years 1967 to 1988**

	Part A Hospital Insurance		*Part B Supplementary Medical Insurance*	
Fiscal Year	*Expenditures (in Millions of Dollars), $*	*Percent Increase Over Previous Year, %*	*Expenditures (in Millions of Dollars), $*	*Percent Increase Over Previous Year, %*
1967	2,597	....	799	....
1970	4,953	4.1	2,196	19.3
1975	10,612	31.6	4,170	27.0
1980	24,288	19.4	10,737	21.8
1985	48,654	15.5	22,730	11.6
1988	52,730	3.8	34,947	13.3

*Source: US House of Representatives, Committee on Ways and Means, 1988.

TABLE 2.—*Real Medicare Disbursements per Enrollee, 1980 to 1989 (in 1988 Dollars)*†*

Fiscal Year	*Total Medicare, $*	*Inpatient Hospital, $*	*Physician, $‡*	*Outpatient Hospital, $*
1980	1,807	1,171	420	95
1985	2,557	1,607	630	142
1988§	2,787	1,552	831	221
1989	2,877	1,568	881	243
	Average Annual Growth Rates			
1980-1985	7.2	6.5	8.4	8.4
1985-1989	3.0	−0.6	8.8	14.3
1980-1989	5.3	3.3	8.6	11.0

*Source: Congressional Budget Office using Health Care Financing Administration data.
†The Gross National Product deflator is used to obtain constant dollars. This table is based on a March 1988 analysis.
‡Includes group practice plans.
§Excludes new benefits under the Medicare Catastrophic Coverage Act.

Real Medicare disbursements per enrollee for physicians' services rose from $420 in 1980 to $881 in 1989, or 8.6% per year (Table 2). The growth rate for hospital expenditures was 3.3% for 1980 to 1989 and actually declined 0.6% for the years 1985 to 1989, following the introduction of prospective hospital payment policies by HCFA in 1983.

Physicians' services account for about 75% of the Part B expenditures. Between 1975 and 1985, total Part B outlays and Part B physician outlays grew more rapidly than hospital expenditures and far more rapidly than the gross national product (Figure 1).

Mitchell and co-workers found that between 1983 and 1986 Medicare expenditures per beneficiary, by type of services, increased 29.5%.[17] By service, the increases were as follows:

Type of Service	*Percent*
Medical care	15.7
Consultations	29.1
Surgery	35.1
Anesthesia	29.6
Radiology	36.4
Laboratory	−1.3
Special tests	66.8

Although an increasingly expensive Medicare program becomes burdensome to the average taxpayer, Medicare enrollees will shoulder a disturbingly large share of this burden. Rice projected that by 1993, if no policy changes

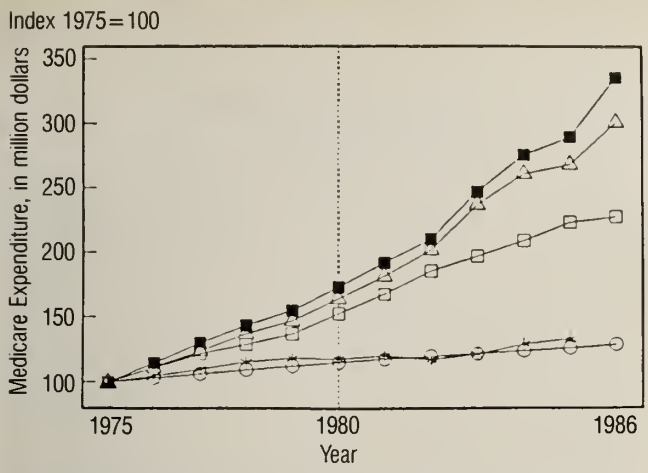

Figure 1.—The graph depicts trends in real Medicare expenditures, 1975 to 1986, indexed to 1975. ✳ = gross national product, ○ = Part B enrollment, □ = Part A (hospital) outlays, △ = Part B (non-hospital) physician outlays, ■ = Total Part B outlays

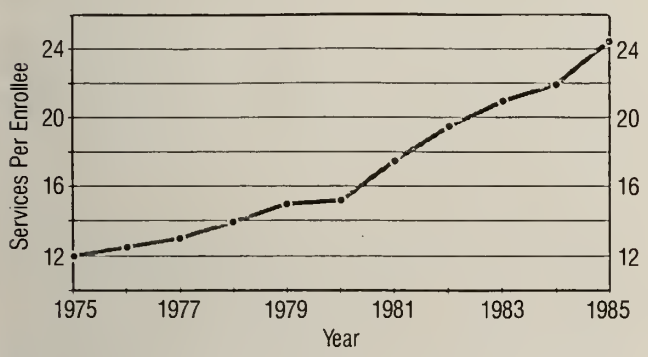

Figure 2.—The total number of Part B services per Medicare enrollee are shown for 1975 through 1985.

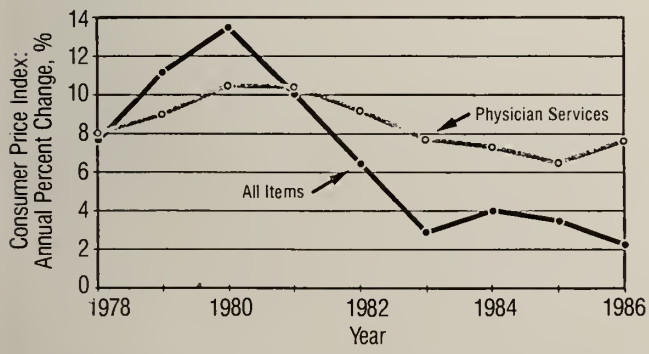

Figure 3.—The graph shows the annual percent change in the Consumer Price Index in all items and in physicians' services, 1978 to 1986.

occur, Medicare enrollees will spend $1,913, or a fifth of their income, on medical expenses including Part B premiums, "Medigap" policies, and unassigned claims.[18] He believes that this is too high a price for ensuring access to health care.

An initial analysis of Part B-approved charges between 1975 and 1985 revealed that expenditures for physicians' services increased because of three primary factors: increases in billed services per enrollee, price increases, and increases in enrollment. When the effect of general inflation is eliminated, it is apparent that volume increases contributed about 2.5 times as much as real fee increases in costs per enrollee for physicians' services.[19]

Volume Increases

The total number of services per enrollee billed by physicians increased from 12 to 16 per year between 1975 and 1980 and from 16 to 24 between 1980 and 1985 (Figure 2).

Mitchell and associates found that between 1983 and 1986 the number of surgical procedures per 1,000 beneficiaries increased substantially for sigmoidoscopy (216%), colonoscopy (120.5%), cardiac catheterization (85.1%), lens replacement (49.9%), total knee replacement (38.5%), and coronary artery bypass graft procedures (19.4%). They found modest increases for hernia repair (9%), total hip replacement (6.7%), and hip fracture (2.3%). For other procedures, the number decreased: transurethral resection (−0.1%), cholecystectomy (−7.9%), carotid thromboendarterectomy (−9.1%), partial colostomy (−16.2%), and permanent pacemaker insertion (−27.9%).[17]

This rising volume, or intensity, may come about in three ways: the packaging of physician services, an increase in the number of procedures, and the involvement of more than one physician.[20] An inflation in the number of procedures is increasingly likely because the number of billing codes used in the Medicare program has grown from 2,000 in 1966 to almost 7,000 today. Although new medical technology is responsible for some of the increase, many codes are simply refinements of existing codes for visits or procedures.

Price Increases

While volume increases have been dramatic in some specialties, price increases have been important for others, including general surgery. Since 1981, price increases for physicians' services have outpaced the consumer price index by a wide margin (Figure 3).

Enrollment Increases

Increases in Medicare enrollment have contributed to rising costs but to a far lesser degree than either volume or price increases. Over the next several decades, the number of elderly persons enrolled in Medicare will grow slowly and will continue to be a relatively minor reason for increased Medicare outlays. Those aged 65 and older currently account for about 12% of the population; that figure will grow to 13% by the year 2000.[21]

Distortions in Payment

With the current CPR system, the commission found distortions in patterns of payment. Payments for procedural services were high relative to evaluation and management services. Payments for imaging, laboratory, surgical services, and many medical diagnostic procedures, such as endoscopy, were high relative to those for office visits and for hospital visits for evaluation and management.

The commission also found erratic patterns in payment by geographic area. Within carrier areas, considerable differences existed between one locality and another. The most striking finding was that the mean value of the allowed charge index in large metropolitan areas—such as New York and Los Angeles—was 23% higher than the national average. For other urban areas, the value of the index was close to the

national average. Rural counties had charges that averaged 10% below the national average. Schieber and colleagues analyzed physician reimbursement rates for 39 medical procedures in 292 local Medicare reimbursement rates and found that the maximum prevailing charge per procedure ranged from three to ten times the minimum charge.[22]

In addition, prevailing charges for the same procedure in seemingly similar communities sometimes differed markedly. In 1984, prevailing charges for a total hip replacement were $4,126 in New York City, $3,094 in Los Angeles, $2,364 in Chicago, and $1,547 in Washington, DC. Among smaller communities the prevailing charge for a total hip replacement was $2,520 in North Carolina and $1,200 in Kentucky. Among rural areas the prevailing charge for a total hip replacement was $2,400 in rural Mississippi, $1,882 in rural Minnesota, and $990 in rural Kentucky.[15]

Physician payments by specialty have proved to be extremely erratic as well. Many physicians feel that differences in payment per unit of time across procedures are unjustifiably large. Differences in the intensity of effort and training do not justify such variation.[23] For example, Hsiao and coworkers estimated that a general surgeon spends 3.4 times as long doing a gallbladder operation as carrying out a comprehensive office visit and devotes 1.8 times as much work per minute but receives 24 times as much reimbursement from Medicare.[24]

Congressional Actions to Control Part B Expenditures

With all of this, it is not surprising that Congress took some actions to control costs. In August 1971, the Nixon administration placed controls on prices of physicians' services, limiting the annual increase to 2.5%. In addition, Medicare placed limits on the growth of reasonable charges. If the increase in actual charges exceeded the allowed increase in reasonable charges, the latter limit was binding. One apparent result of the price controls was an increase in the volume of billed services, and thus expenditures continued to rise rapidly. Medicare spent 29.5% more per beneficiary for physicians' services in 1986—the last year of the fee freeze—than three years earlier.[17]

In 1976 the provisions of the Social Security Amendments of 1972 were implemented. These required that updates of prevailing charges not exceed the rate of increase in the Medicare Economic Index, an input price index for physicians' practice costs. The Medicare Economic Index has served to slow the rate of increase in physician payments.

Since 1984, congressional efforts to slow the rate of increase in Part B expenditures have included a fee freeze that lasted two years; substantial reductions in the number of overpriced procedures; limits on physicians' ability to charge patients the difference between their submitted charge and Medicare's maximum actual allowable charge; incentives to increase the acceptance of Medicare payments as payment in full (assignment); and other measures.[15] While some of these policies may have achieved a minimal degree of success, together they did not significantly slow the growth in Part B outlays.

In addition to changes in payment rates and limitations on balance billing, payment reform has also focused on creating an infrastructure for further policy changes. In the mid-1980s Congress mandated a study of a resource-based relative value scale and created the Physician Payment Review Commission.

Physician Payment Review Commission—Mandate and Recommendations

The Physician Payment Review Commission was created by Congress in 1986 to advise it on reforms in the methods used to pay physicians for services to Medicare beneficiaries. The Congress expanded the commission's mandate in 1988 to include a consideration of policies to moderate the rates of increase in expenditures and the use of services.

Consistent with its mandate, the commission developed a comprehensive set of proposals to change the pattern of relative payments to physicians by Medicare and to slow the rate of increase in program costs so that they are affordable to both beneficiaries and taxpayers:

- To rationalize payments by Medicare, the commission proposed a Medicare fee schedule based primarily on resource costs.
- To limit beneficiary financial liability, it recommended limits on balance billing.
- To control the growth in expenditures, the commission proposed the use of expenditure targets and increased research on the effectiveness of medical services and the development of practice guidelines.[15]

Medicare Fee Schedule

The commission proposed that the current customary, prevailing, and reasonable method of paying physicians be replaced by a Medicare fee schedule based primarily on resource costs. It also recommended that the Medicare fee schedule cover all specialties, including radiology and anesthesiology, for which separate Medicare fee schedules now exist. The policies adopted by Congress in the Omnibus Budget Reconciliation Act of 1989 provide for radiologists, anesthesiologists, and pathologists to be paid on the basis of specialty-specific fee schedules. For radiology and anesthesiology, the current fee schedule (radiology) or relative value guide (anesthesiology) will be used with modifications to make relative values consistent with the new Medicare fee schedule. For pathology, the Secretary of Health and Human Services is to develop a fee schedule by January 1, 1991.

A fee schedule consists of the following:

- A *relative value scale* that indicates the value of each service or procedure relative to others;
- A *conversion factor* that translates the relative value scale into a fee for each service; and
- A *geographic multiplier* that indicates how payment for a service is to vary from one geographic area to another.

Relative value scale. The commission recommended that the relative value scale comprise two cost elements: relative physician work and practice costs. With respect to relative physician work, the commission favors the use of the methodology for estimating relative physician work developed by Professor William Hsiao and his colleagues at Harvard, with refinements based on current work by Professor Hsiao and analyses currently under way by the commission. Hsiao and associates directly measured, through physician surveys, about 350 of the high-volume services and procedures within 18 different medical and surgical specialties. For each of the

specialties, 160 randomly selected physicians from across the United States were surveyed. They found excellent agreement among the physicians on the degree of intensity and time associated with individual procedures.[24-32]

The commission, the American Medical Association, and others carefully evaluated the pioneering work by Hsiao and colleagues to develop a resource-based relative value scale. The commission found the methodology for estimating relative physician work to be sound and drew heavily on it in developing its relative value scale for the Medicare fee schedule. The commission's evaluation calls for additional research to be undertaken by Hsiao and the commission staff to strengthen the results of the study. Most of these tasks are underway.

The commission developed a formula for incorporating practice costs into the relative value scale that allows for overhead to be calculated independently from physician work.

Insurance coverage for professional liability represents a major cost to physicians that varies substantially by specialty and geographic area. To assure that the fee schedule adequately accounts for differences among risk classes—for instance, physicians doing no surgical procedures versus thoracic, vascular, and orthopedic surgeons—and localities—such as Florida or Idaho—used in setting premium rates, the commission recommended that professional liability insurance premiums should be treated as a separate practice cost factor.

Conversion factor. The conversion factor transforms the relative value scale into a schedule of dollar payments for each service. To have funds available to increase payments for evaluation and management services, while decreasing payments for surgical services, laboratory services, and imaging, it was recommended that the initial conversion factor be set so that outlays for physicians' services projected under the Medicare fee schedule would be the same as those projected under the current payment system.

Geographic multipliers. The commission recommended that a geographic multiplier be used to modify payments by geographic area. The modifier should reflect variations in overhead costs of practice. With this policy, physicians in different parts of the country providing the same services would receive the same net income from Medicare. This policy would reduce substantially the magnitude of geographic variation in fees. The commission has yet to define the geographic areas to be used.

Specialty Differentials

The commission recommended that when a service provided by physicians in different specialties is essentially the same, the payment should be the same. Therefore, specialty differentials—differences in payment to physicians of different specialties for the same procedure code—would be eliminated under the fee schedule.

Coding

A national fee schedule requires that the codes for physicians' services be interpreted uniformly by all physicians and carriers. Only then can accurate relative values be assigned to each service so that fees reflect the resource costs associated with providing that service. The commission's recommendations call for changes related to coding in two important areas: surgical global services and evaluation and management services.

Surgical global services. With the unanimous agreement of a consensus panel made up of surgeons and carrier representatives, the commission developed a policy defining which services associated with an operation are to be included in the global payment for surgery and which are to be paid separately.

Evaluation and management services. Physicians cannot accurately use the current codes for evaluation and management services (commonly referred to as visit codes) to reflect their time and work because the levels of service—that is, brief, intermediate, or comprehensive—are not precisely defined. The commission recommended that time be incorporated into the definitions for visit codes. This coding reform would allow more accurate relative values to be assigned to these services and help physicians use the codes properly. Carriers would also have a way to determine whether physicians were billing correctly for these services.

Transition

The commission recommended a transition from the current payment system to full implementation of the Medicare fee schedule. This would give physicians and beneficiaries time to adjust, allow for midcourse corrections, and increase the chances that private payers will change their policies as Medicare changes are being implemented.

The transition must be designed to avoid disrupting the administration of the program by carriers. The commission's plan called for a transitional fee schedule that would retain customary and prevailing charge screens. It would base changes in prevailing screens on the difference between current payments and those projected for the Medicare fee schedule.

The legislation enacted by Congress in December 1989 calls for the Secretary of Health and Human Services to publish a model fee schedule by September 1, 1990, and to review and revise the relative values at least every five years. The fee schedule will be implemented beginning January 1, 1992.

The commission did not make its recommendations for a Medicare fee schedule in a vacuum. In developing its recommendations for a Medicare fee schedule, the commission benefited from previous studies of physician payment by a number of researchers.[1,3,4,6,14,19,33-37] The research that most influenced the development of the Medicare fee schedule by the commission was the work carried out by Hsiao and colleagues at Harvard.[24-32]

Assignment and Balance Billing

Currently Medicare limits beneficiaries' financial responsibility for charges in excess of what it allows on unassigned claims through its maximum actual allowable charge. The commission recommended replacing the limits on maximum actual allowable charges by establishing limitations on charges for unassigned claims to a fixed percentage of the fee schedule amount. Congress adopted this recommendation and set balance billing limits at 125% in 1991, 120% in 1992, and 115% in 1993. The commission also recommended continuing the Participating Provider and Supplier Program and its payment differential that provides higher fees to participating physicians.

Policies to Slow Increases in Expenditures

The rapid rate of growth of spending for physicians' services in Medicare has led to unsustainable increases in federal budget outlays and in beneficiary premiums and copayments. If spending continues to grow so rapidly that it consumes an increasing percentage of the gross national product and the federal budget, it will increasingly divert federal funds from education, investments to increase productivity, and other health and social needs.

Expenditure Targets

The commission proposed an expenditure target to slow the rate of growth of Medicare program costs by relating the annual update of the Medicare fee schedule conversion factor to the rate of increase in expenditures. It would provide a collective incentive to physicians to slow the growth in the volume of services provided Medicare patients by reducing services of little or no benefit. It would give greater impetus for the medical community to collaborate with the Medicare program to increase knowledge of the effectiveness of services, to use this knowledge to improve the appropriateness of medical practice, and to strengthen peer review. Expenditure targets would both send a message about the need to slow the rate of increase in program and beneficiary outlays and provide physicians constructive ways to respond.

The commission recommended the establishment of a national expenditure target for physicians' services under Part B to determine annual conversion factor updates under the Medicare fee schedule. The target would reflect increases in a reformulated Medicare Economic Index, growth and aging of the enrollee population, and a decision concerning the degree to which expenditure growth should exceed these factors. The update would be increased or decreased to reflect differences between actual and targeted expenditure increases.

The commission recommended beginning with a single target at the national level but provided Congress with several alternatives, including targets established for states or carrier areas. The American College of Surgeons supported a separate target for surgical services, while the American Medical Association opposed the expenditure target proposal.

It was the commission's opinion that expenditure targets would not alter the financial incentives for individual physicians and their patients. Rather, the incentives would fall to the physician community, which could respond through education and support of the existing infrastructure of medical review. For example, the American Medical Association and other national specialty societies could develop practice guidelines and disseminate them. They could provide technical assistance to carriers and professional review organizations in developing criteria for peer review and political support for sanctioning physicians who persisted in providing inappropriate and poor quality care.

The commission also felt that lessons learned from the Canadian experience of instituting expenditure targets could ease the application of this policy to the Medicare system. Based on their analysis of Canada's experience, Lomas and colleagues recommended that both price and volume controls be introduced simultaneously and that the rules for implementing the expenditure target be decided on prospectively. They also advised Medicare to create a joint payer-physician committee to scrutinize specific clinical areas of usage increase and their impact on quality of care.[38]

In lieu of the expenditure target proposed by the commission, Congress established a volume performance standard to determine the annual fee update for physicians' services. Each fiscal year the Secretary of Health and Human Services will recommend to the Congress acceptable performance standard rates of increase for expenditures and volume of physicians' services. Congress will then establish performance standard rates of increase. If Congress fails to act on the Secretary's recommendations, the performance rates of increase will be determined through an automatic default mechanism.

Effectiveness Research and Practice Guidelines

Physicians cannot make significant improvements in the quality and effectiveness of medical practice without substantial government support. The commission recommended a substantial increase in federal funding for research related

TABLE 3.—*National Mean Allowed Charges in 1988 for Selected Procedures by the Medicare Fee Schedule and Customary, Prevailing, and Reasonable (CPR) Charge System**†

Code	Procedure	Medicare Fee Schedule, $	CPR System, $	Change, %
Evaluation and Management				
90050	Limited office visit	29	23	+24
90260	Intermediate hospital visit	40	30	+35
90620	Comprehensive consultation	104	93	+13
Surgery				
27130	Total hip replacement	1,955	2,404	−19
33512	Coronary artery bypass	2,816	3,894	−28
52601	Prostatectomy (transurethral resection)	920	1,128	−18
Diagnostic				
70470	Contrast computed tomographic scans of head	78	113	−31
71010	Roentgenographic examination of chest, one view	10	12	−20
93000	Electrocardiogram, complete	25	35	−30

*From Lee et al, 1989.[39]
†Fees are for procedures performed by the most common specialty in the most common place of service.

TABLE 4.—*Percent Change in Medicare-Allowed Amounts By Specialty**

Specialty	*% Change*
Medical	
Internal medicine	+18
Family practice	+40
Dermatology	+ 1
Surgical	
Ophthalmology	−16
General surgery	−10
Urology	− 4
Thoracic surgery	−19
Hospital-Based	
Radiology	−25
Pathology	−24

*From Lee et al, 1989.[39]

TABLE 5.—*Percent Change in Medicare-Allowed Amounts By Area**

Area	*Specialty Group*	*% Change*
Very large metropolitan	Medical	− 1
	Surgical	−26
	All physicians	−14
Small metropolitan	Medical	+26
	Surgical	− 7
	All physicians	+ 3
Large rural	Medical	+31
	Surgical	− 5
	All physicians	+13

*From Lee et al, 1989.[39]

to the effectiveness and appropriateness of medical practices. Such funding should also support the development and dissemination of practice guidelines resulting from new research to provide physicians with the tools they need to improve the quality of care. Physicians need to know more about which of the available diagnostic tools work and which patients would benefit from particular therapies. This knowledge is essential if the number of unnecessary and inappropriate services is to be reduced.

Research also is needed to determine the medical outcomes and costs of alternative medical practices and procedures. In addition, more knowledge is needed to determine the best ways to organize and provide care. This research should include clinical trials, epidemiologic studies of data generated by clinical practice, analyses of the cost-effectiveness of alternative ways to organize care, and an assessment of techniques used in managed care to influence physicians' clinical decisions.

Practice guidelines have been developed in recent years to synthesize what is known from research and the judgments of practicing physicians into a form that can be readily used. To date, practice guidelines have been used primarily for education and training. The commission recommended that the federal government actively encourage the development and dissemination of practice guidelines so that they are incorporated into physicians' practices, made available to patients, and used as the basis for coverage and payment, as well as for medical review criteria by hospital medical staffs, carriers, and peer review organizations.

The federal government also has a role as administrator of Medicare. The Health Care Financing Administration should reinforce the importance of basing medical review on sound criteria by assisting professional review organizations and carriers in selecting and using review criteria that are consistent with practice guidelines.

Utilization Review

The commission supports the current efforts by HCFA to move toward a more comprehensive approach to medical review and called for further action to strengthen the review process.

Effects on Physicians and Beneficiaries

The commission constructed several simulation models to estimate the impact of the Medicare fee schedule on physicians and beneficiaries. Using the national mean allowed charges in 1988, the commission found that under the Medicare fee schedule, changes in payment would range from plus 35% for an intermediate hospital visit to minus 31% for contrast computed tomographic scans of the head (Table 3).[39] Payment for most evaluation and management services would increase, while most of those for surgical procedures and diagnostic procedures would decrease.

The effect on major specialties reflects this change in relative payments (Table 4).[39] Medicare payments to family practice physicians would increase by 40%, for internal medicine specialists by 20%, and for dermatologists 1%, but payments to thoracic surgeons would decline by 19%.

The Medicare fee schedule would also change the distribution of payment among geographic areas (Table 5), with higher payments to rural areas and lower payments in large urban areas.[39] The impact of the changes in the relative value of services and procedures and of correcting geographic inequities will vary across the country.

Conclusion

Four years ago the Congress created the Physician Payment Review Commission with a mandate to suggest policies to rationalize Medicare payment for physicians' services and to slow the rate of growth of expenditures for these services.

The commission believes that a Medicare fee schedule will serve to rationalize payments by tying them to resource costs. It will be simpler and easier to understand for both physicians and beneficiaries. It will promote better care and provide additional financial protection for beneficiaries.

Volume performance standards will help slow the increase in Medicare expenditures so that we as a society can meet other pressing social needs. Limits on balance billing and continuation of the Participating Provider and Supplier Program will protect beneficiaries. Increased effectiveness research and practice guidelines will provide us with the knowledge and means to manage available health care resources more wisely.

With the changes proposed by the Physician Payment Review Commission and enacted by Congress, the commission believes that Medicare can continue to meet the medical needs of our elderly and disabled citizens.

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Epitomes
Important Advances in Clinical Medicine

Preventive Medicine and Public Health

The Scientific Board of the California Medical Association presents the following inventory of items of progress in preventive medicine and public health. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in preventive medicine and public health that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Preventive Medicine and Public Health of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Advances in Prenatal Screening

PRENATAL SCREENING TESTS address two types of problems: maternal diseases that can affect the health of the fetus or newborn, and fetal anomalies or diseases that may or may not have effective treatments. Examples of screening tests for maternal diseases include maternal hemoglobin, rubella titer, Rh factor, tuberculin skin testing, and tests for sexually transmitted diseases. An example of testing for fetal defects is amniocentesis for women older than 35 years.

In recent years, several other maternal diseases that can affect the fetus have been recommended for screening. In 1988 the Centers for Disease Control recommended that all pregnant women receive hepatitis B screening regardless of their risk status. As many as 65% of mothers who test positive for the hepatitis B surface antigen have no known risk factors, and if the mother is positive there is a 90% chance of neonatal acquisition with the attendant morbidity and mortality. Prompt immunization of infants with exposure to hepatitis B can be protective. The Second International Workshop-Conference on Gestational Diabetes and the American Diabetes Association recommend routine 50-gram glucose tolerance testing of all pregnant women between 24 and 28 weeks of pregnancy, while the American College of Obstetricians and Gynecologists recommends screening only for those older than 30 years. Those at high risk for gestational diabetes (history of macrosomatia or of stillborn pregnancy) should be screened with the 50-gram glucose tolerance test at the end of the first trimester. About 25% of women may be asymptomatic carriers of group B *Streptococcus,* and this remains the most common cause of neonatal sepsis in the United States. The protocol for minimizing this risk of neonatal sepsis includes screening all women for the carrier state at 28 weeks' gestation. Those women with cultures positive for group B streptococci are treated only if they fall into one of the following high-risk groups at the time of delivery: preterm delivery before 36 weeks of gestation, premature rupture of membranes more than 12 hours before the beginning of labor, prolonged rupture of membranes more than 24 hours before delivery, a history of other infants previously infected with group B streptococci, signs of amnionitis, or mother receiving immunosuppressant treatment. Earlier treatment does not provide prolonged protection, and treatment of uncomplicated term infants before delivery does not reduce the incidence of sepsis. Infants of mothers who are carriers but who did not receive treatment are monitored for sepsis but not routinely treated.

For one possible neonatal infection, less screening is now recommended. Serial cervical cultures for herpes simplex virus have not been useful for detecting those at risk for transmitting the virus during vaginal delivery. Current guidelines suggest confirming the diagnosis by culture of visible lesions at any time during pregnancy, then a careful examination during labor for any sign of active lesions. If none is present, vaginal delivery is indicated.

Some of the tests that attempt to detect fetal anomalies or congenital diseases offer hope for the prenatal treatment of the fetus. Others offer the option of therapeutic abortion or advanced preparation for a compromised fetus. For example, California requires that maternal serum α-fetoprotein screening be offered at between 15 and 20 weeks for neural tube defects. Ultrasonography and amniocentesis can confirm the anomaly and better clarify the severity. The parents then can make an informed decision regarding the management of the pregnancy. Maternal serum α-fetoprotein abnormalities can also provide clues for trisomy 21 and treatable problems such as gastroschisis. The risk of unnecessary intervention can be avoided if the α-fetoprotein screening is done with the cooperation of a dedicated coordinator, skilled ultrasonographers, and perinatologists. As another example, the screening of mothers at risk for the human immunodeficiency virus can anticipate the need for postnatal infection control precautions or can prepare the parents and physicians for the need for intensive attention to the newborn.

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Medication Misuse by the Elderly

THE MISUSE OF MEDICATIONS by the elderly falls into two major categories. One is noncompliance with or nonadherence to a drug therapy regimen. This may occur in as many as a third to half of the elderly patients taking prescription drugs. The reasons found for noncompliance are poor communication with health professionals and impaired cognitive status. As many as 90% of cases of nonadherence to prescribed treatment can take the form of underadhering or taking too little medication. One study found that as many as 70% of the elderly patients may actually alter their intake of prescribed medication intentionally for a variety of reasons, including an attempt to minimize adverse effects. Drug misuse by the elderly can also occur as a result of a pursuit of symptomatic relief from unrecognized depression and from chronic ailments of advancing age. A physiologic dependency on tranquilizers, sedatives, and analgesics can easily develop in an elderly patient with undiagnosed depression. Therefore, the presence of depression should be carefully screened for when evaluating drug use in the elderly.

Another area of drug misuse by the elderly is the use of outdated medications or medications from other members of the family or neighbors. In one study of 334 low-income elderly and disabled persons living in a high-rise building, 75% of the subjects were found to be currently using prescription drugs and 82% were using nonprescription drugs. Respondents used an overall average of 4.5 prescription and nonprescription drugs regularly. About 51% of the interviewees stored one or more current prescription drugs and 67% stored one or more noncurrent prescription drugs. The average number of all medications per home was 8.4, whereas the average number of nonprescription medications was 2.6. In this study, 24% of the participants underused medication, 7% did not know the purpose of their medication, and another 7% shared their medication with other persons. In all, 6% used outdated prescription medication, and 4% overused their medication as prescribed. As shown by these statistics, the elderly usually do not consider nonprescription drugs to be medications and frequently omit these when mentioning what medications they are taking. There are also a lot of extra medications being stored at home that are not being accounted for on office visits to a physician.

In another study of 356 persons selected at random from the community, there were 125 cases of medication misuse. The most frequent types of misuse were inappropriate dosage, indications for use, or usage level. Most common classifications of drugs misused are the psychotherapeutic drugs, diuretics, and cardiovascular drugs. There seems to be no association between the misuse of medication and gender, age, income, or education. Misuse, however, is positively correlated with the number of drugs being taken. There was a significant difference in misuse between those persons who took psychoactive medications and those who did not. Persons who are taking psychoactive drugs are more likely to misuse drugs.

The problems of medication misuse by the elderly can frequently be addressed by better assessment and more drug information. Pharmacists can assume a more active role in patient education, and practitioners may consider providing community-based health and drug information education programs. Another way to address this problem is to make sure elderly patients bring all of their home medications into their physician's office when they are being evaluated. Another approach to assessing medication use is to do a home visit. It has been shown that home visits can be useful in providing additional information about compliance and drug use by the elderly. Finally, compliance can also be enhanced by clarifying written and verbal instructions, reducing the number of drugs, simplifying the drug dose schedule, and providing devices to assist patients with accurate self-administration.

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Pesticides in Food

THE RECENT NATIONAL ATTENTION focusing on the issue of food safety prompted us to examine two studies of the actual occurrences of pesticide-related food contamination to see how well the incidence data corroborate some of the concerns.

In the first study, the Environmental Protection Agency (EPA) commissioned the National Research Council of the National Academy of Sciences to estimate the oncogenic risks from pesticides in the diet and to examine regulatory policies for oncogenic pesticides in raw and processed foods. The National Research Council selected 28 pesticides from the 53 determined or suspected by the EPA to be oncogenic and estimated the cancer risks from the diet. The estimated theoretical added lifetime risks for the daily consumption of some of these pesticides were greater than one in a million. When the National Research Council's report was released, there was a tendency to overlook or inadequately emphasize the theoretical nature of the risk estimates because it was assumed that pesticide residues were always present at the tolerance levels and that all the food crops had been treated with the pesticides. Actually levels of residues detected by monitoring programs are typically below the legal tolerances, and many crops are not treated with the pesticides in question nor do they show any detectable levels of residues. Therefore, these risk estimates should not be construed as true consumer risks, but they provide an index for ranking pesticides for regulatory attention.

In the second study, the Natural Resources Defense Council assessed the health risks of pesticide residues in food to preschool children based on an evaluation of two health effect end points, cholinesterase inhibition and cancer. One major assessment was that daminozide (trade name Alar), due primarily to its hydrolysis product, 1,1-dimethylhydrazine, which occurs in food, contributes to 85% of the estimated cancer risks. The ensuing public concern regarding daminozide residues in apples and processed apple products resulted in the temporary exclusion of these food items from school lunch programs in several cities. This action was not justified because there was no imminent hazard identified on the basis of the available data. The report brought the important and previously neglected issue of childhood exposure to the attention of the EPA, but the Natural Resources Defense

Council failed to emphasize that food safety is not achieved by restricting the availability of fruits and vegetables or their intake. In this connection, it is of concern that a potential carcinogen was used in children's food for more than 20 years before the manufacturer was required to conduct adequate carcinogenesis bioassays. Studies in the 1970s suggested that daminozide is carcinogenic in laboratory animals, and new data on 1,1-dimethylhydrazine are strongly suggestive. The issue of daminozide exemplifies the need for more stringent health testing of pesticides before they are permitted to be used. Use restrictions started in 1985, and the manufacturer is in the process of withdrawing the product.

The illegal use of pesticides has been responsible for several acute illness episodes in the western United States. In 1985 aldicarb residue in watermelons caused nausea, vomiting, diarrhea, profuse sweating, excessive tearing, muscle fasciculations, and bradycardia. The treatment in the most severe cases was to administer atropine sulfate.

Endrin, an organochlorine insecticide, caused five cases of poisoning in 1988 in Orange County, California. These may have been caused by deliberate tampering with a commercial product—a snack consisting of a corn tortilla wrapped around a meat filling sold in sealed plastic bags. The symptoms included nausea, dizziness, and seizures. Since 1984, endrin is not registered for agricultural purposes or manufactured in the US, but supplies of the pesticide remain, and other countries continue to use and manufacture the chemical.

In summary, to our knowledge there have been no confirmed cases of acute poisoning from ingesting legally applied pesticides on food in California. On the other hand, health officials and physicians should be aware of signs and symptoms associated with pesticide overexposure and the existing reporting system for pesticide-related illness in order to assist in identifying cases, treatment, sources, and appropriate control and risk management measures.

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The Epidemic of Childhood Drowning

THROUGHOUT THE WESTERN STATES, drowning surpasses motor vehicle occupant injuries as the leading cause of death of children ages 1 to 4 years. For every child who drowns, about two or three children survive severely brain damaged and an estimated eight to ten near-drowning victims are seen in emergency departments. Of the near-drowning victims treated in emergency departments, 80% are admitted to hospitals for further treatment or observation. With the widespread use of ventilators, intensive care units, and advanced cardiopulmonary resuscitation (CPR) techniques, many of the children who would have died before the mid-1970s now survive. As a result, there is a growing number of children who survive submersion events with severe neurologic damage due to anoxia but whose hearts and lungs recover. The actual size of the population is not known, but in California they constitute the largest group of children entering state institutions for long-term care with profound acquired brain damage. California alone spent more than $10 million in 1988 to care for these children.

Although children can and do drown in any body of water, the majority of incidents in this age group occur in residential swimming pools. Studies have shown that half of these drownings occur at a child's own house or apartment, 36% at the home of a friend, neighbor, or family member, and only 7% at other sites, including public pools. Children appear to be at greatest risk between the ages of 1 and 3 years. At this age, children cannot be made "water safe" through swim lessons because they lack sufficient strength, gross motor coordination, retention of learned skills, and judgment.

In the most common scenario, a child thought to be safe inside the house gains access to the pool while a parent or caregiver is momentarily distracted by the telephone or household chores. The whole event is silent, and the amount of time the child has been missing is unknown. Because neurologic damage occurs quickly with a lack of oxygen, prevention efforts have focused on constructing barriers to block access to pools, alarms to warn the caregiver, educating parents regarding the danger, and CPR training.

No one foolproof method of preventing access to a pool has been found. Thus, experts recommend that layers of protection be installed, including as many of the following as are feasible:

- Four-sided fencing that separates the pool from the house, is 1.5 m (5 ft) tall, hard to climb but easy to see through, and with gates with self-closing, self-latching mechanisms that cannot be reached or operated by a young child;
- ASTM [American Society for Testing and Materials]-approved safety covers (covers not designed for safety pose additional hazards, and those not attached to the pool deck are dangerous);
- Door, window, and pool alarms; and
- Window and door locks.

The ultimate challenge is to develop protective technology that is both feasible and foolproof. In the meantime, physicians should counsel parents regarding the dangers of residential pools and the need for layers of protection, close supervision, and CPR training. The circumstances surrounding a submersion event should be noted in the medical record to assist prevention research and the recognition of causal patterns. Finally, physicians and public health professionals should join with drowning prevention programs to see that four-sided fencing, pool safety covers, or both, are incorporated into standard building codes for implementation at the time of pool construction or the sale of a home.

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Injuries—The 'Neglected Disease of Modern Society'

INJURIES ARE the leading cause of death and disability of Americans between the ages of 1 and 44 years old. Each year more than 142,000 people are killed and 62 million others seek medical attention because of an injury. The cost of injuries, including medical expenses, lost wages, and property damage, was estimated at $143.4 billion in 1988.

While medicine has made great strides in combating infectious diseases, injury mortality has remained fairly constant. Until recently "accidents" were assumed to be caused by random or chance events and, as such, were considered outside the realm of prevention. We now know that injuries occur in predictable and regular patterns with identified agents and vectors. They are caused by human interaction with the environment and are strongly linked to a person's age and development. Motor vehicle occupant injuries affect all age groups and cause about half of all injury deaths and disabilities. In addition, injury mortality in the western states tends to cluster as follows: suffocation or choking and homicide deaths among infants; residential pool drownings among toddlers; pedestrian and motor vehicle occupant injuries among elementary school-age children; motor vehicle occupant and violent (homicide and suicide) injuries among teens; motor vehicle occupant, drug overdose, and violent injuries among adults; and falls, motor vehicle occupant, and suicide injuries among the elderly.

In recent years, the injury problem has begun to receive national attention, and the scientific discipline of injury control has been established. Injury research and control efforts have escalated, and a national lead agency has been established at the Centers for Disease Control. A number of effective prevention strategies have been identified as follows:

Injury Type	*Intervention*
Bicycle	Bicycle helmets
Burns	Smoke detectors, sprinklers, self-extinguishing cigarettes, flame-retardant sleepwear, water heaters preset to 49°C to 54°C (120°F to 130°F)
Choking	Toy and food regulations, first-aid treatment of choking
Drowning	Four-sided fencing, pool safety covers
Falls	Window bars,,hand rails, child-resistant barriers
Firearms	Gun control
Motor vehicle occupant	Car safety seats, seat belts, air bags
Motorcycle	Motorcycle helmets
Poisoning	Child-resistant safety caps, packaging in nonlethal doses
All injuries	Emergency medical services and trauma systems

The challenge before us is to implement these strategies through education, legislation, enforcement, and medical and public health leadership. In addition, we need to document in the medical record the circumstances of the injury event to determine causal patterns and prevention strategies.

Injury control should be addressed by a systems approach. Public health professionals should use vital statistics and hospital and trauma system data to define the problem within their region; mobilize community resources and persons to address problems identified; use environmental, legislative, and educational approaches for prevention; evaluate the impact of prevention efforts; and disseminate evaluation results to others to incorporate in program planning.

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The Preventive Use of Zidovudine in Asymptomatic HIV Infection

THE US PUBLIC HEALTH SERVICE estimates that between 1 and 1.4 million Americans are infected with the human immunodeficiency virus type 1 (HIV-1), the causative agent of the acquired immunodeficiency syndrome (AIDS). The inescapable conclusion drawn from studies of the natural history of HIV-1 infection is that in the absence of an effective intervention, the overwhelming majority of those infected will progress to have profound helper T-cell depletion and will die of AIDS.

Zidovudine (formerly azidothymidine; AZT) is currently approved for use for a narrow category of patients with advanced HIV disease. In August 1989, the momentum for expanding the indications for zidovudine use accelerated by a quantum leap. Two national placebo-controlled trials in mildly symptomatic and asymptomatic patients with HIV were modified short of completion by the National Institutes of Health AIDS Clinical Trials Group because of conclusive evidence for zidovudine's benefit and minimal toxicity. These results should lead to major changes in patient and physician attitudes towards HIV testing, T-cell monitoring, and treatment of this infection at all its stages. Before August 1989, the use of zidovudine in mildly symptomatic or asymptomatic HIV infection was an area of controversy among experts. In the months since the findings were made public, a new consensus is emerging.

The two studies enrolled two distinct, well-defined categories of patients with HIV disease, early AIDS-related complex (ARC), and asymptomatic seropositivity, respectively. Both studies showed the efficacy of using zidovudine in slowing the progression to symptomatic disease, AIDS, or ARC. The study in asymptomatic seropositive persons enrolled 3,200 volunteers and compared the use of placebo with that of zidovudine at two dose levels, 500 mg per day and 1,500 mg per day. For participants with CD4 (helper T-lymphocyte) counts of less than 0.5×10^9 per liter (500 per μl) in both zidovudine groups, the rate of progression over two years was cut by 50%. The adverse effects of the 500-mg-per-day regimen were minimal, the most notable being a 3% incidence of major anemia. While progression to symptomatic stages was not invariably stopped, the studies indicate that at least the short-term outlook for patients with asymptomatic or minimally symptomatic HIV disease can be dramatically improved. Information on the duration of the

protective effect should eventually be available from long-term follow-up of these cohorts.

The US Public Health Service has estimated that 600,000 patients should be offered early treatment with zidovudine based on the findings of these two studies. Because of a reluctance to undergo HIV testing, many may be still unaware that they are infected. Most patients with HIV infection in this country became infected in the early 1980s. In view of the median interval of 9.5 years between the infection with HIV and the development of AIDS, the medical profession has a relatively brief window of opportunity to implement any intervention that slows the progression of HIV disease. The two studies prove that zidovudine, while not invariably effective, when administered at an early stage of disease can have a definite impact. The new data make it a particularly opportune time for health professionals to focus on HIV risk assessment and testing with all of their patients and to specifically review histories of sexual activity, substance abuse, and blood product transfusion. If physicians wait for the zidovudine package insert to be changed, they will deprive many patients of the opportunity to benefit from these new findings.

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Preventing Lead Poisoning in Children

THE CURRENT STANDARD for blood lead concentrations in children is 25 μg per dl. Researchers throughout the world, however, have recently shown that a blood lead level of as low as 15 μg per dl during gestation and infancy is associated with subclinical neuropsychological impairments, particularly in verbal learning, with an average of four IQ points being lost.

Recent population-based surveys of children younger than 6 years living in older urban areas in Alameda and Los Angeles counties, California, indicate that many children are exposed to lead—blood concentrations greater than 25 μg per dl in 1% to 2% and greater than 15 μg per dl in 10% to 20%. Substantial lead contamination was found in indoor and outdoor paint in Alameda and Los Angeles county study areas (Los Angeles results unpublished) and in soil in the Alameda County area. An additional study is planned for Sacramento County, California. Indoor paint contamination occurs because many homes were built before the 1950 voluntary industry standard and the 1977 federal standard for lead in house paints. Soil contamination is from auto emissions, exterior paint, and industrial sources.

The California studies only tested paint from homes where paint was chipping or flaking. An additional hazard is present in homes where lead-based paint is in good condition but where renovation can lead to the spread of paint dust and chips into the home environment and exposure to children. In the past few years, several cases of such exposures have come to the attention of the California Department of Health Services; in most cases, the children involved were asymptomatic. Parents and contractors need to be educated about the proper techniques for removing paint that can prevent household contamination.

Additional lead hazards to children are posed by dangerous hobbies around the home (common ones are making stained glass and melting down lead shot to make fishing weights or model figures); ethnic folk remedies used for the treatment of diarrhea (used by such diverse ethnic groups as Hispanics, Southeast Asians, and South Indians); lead in drinking water from leaching from leaded solder, particularly from homes built in the past five years; and take-home exposures from parents who work in lead-contaminated workplaces such as radiator repair shops and smelters.

Public Health Approaches

The two basic approaches that have been proposed involve screening the children and then cleaning up the environment where lead exposure has been found in children or searching for possible environmental sources and regulating exposure.

Lead screening. Childhood lead screening programs are designed to identify elevated blood lead levels in children and investigate and remove lead from contaminated home environments. The US Centers for Disease Control recommend annual screening for children younger than 36 months living in older, dilapidated housing. Screening is not conducted in most of the western states.

The California Department of Health Services has undertaken educational efforts to provide physicians with the most up-to-date information about lead exposure and to encourage them to increase their efforts to screen for lead poisoning. These efforts need to be increased. Access to information, however, is not the only barrier to physician involvement in lead screening. One barrier is motivation; in most cases no medical intervention is needed, other than identifying potential source(s) of exposure by history, giving nutritional guidance, and educating parents. Possibly some form of incentive could be devised to motivate physicians to screen. The second barrier is technical: when screening for blood lead levels below 40 μg per dl, the erythrocyte protoporphyrin screening test has a poor predictive value, and capillary blood lead specimens give a high false-positive rate. Providers do not routinely use venipuncture. Technologic breakthroughs in lead screening that would allow a more acceptable process of specimen collection would help overcome this barrier. In the absence of incentives, the development of new, more feasible technologies for screening, or a requirement that screening be done, it is uncertain what role physicians will take in addressing the problem in the future.

Environmental regulation. To address the problem of lead-contaminated houses, it is not necessary to first identify lead exposure in children. For example, a program could identify and decontaminate lead houses, using strategies to encourage owner participation. The costs are unknown, however, and the methods for lead removal need further study.

For other sources of lead exposure, additional regulatory and educational approaches could be undertaken. Lead is still used by the canning industry, with a voluntary standard for lead in solder. The phaseout of lead in gasoline has been only partially accomplished. Lead-based paint and solder are still on the market and are occasionally inappropriately used in homes. Laws restricting workplace lead exposures have a

number of exemptions and are only partially enforced. Many household exposures could be prevented by educating parents about lead in paint, pottery, ethnic remedies, and home hobbies.

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The Tuberculosis and HIV Connection

EVIDENCE SUGGESTS that clinical tuberculosis eventually develops in a high percentage of persons infected with both the human immunodeficiency virus (HIV) and *Mycobacterium tuberculosis.* Tuberculosis often precedes other opportunistic diseases in patients with the acquired immunodeficiency syndrome (AIDS), but tuberculosis-infected patients who survive the first episode of AIDS are at a high risk of clinical tuberculosis developing. This has contributed to the increase in the number of tuberculosis cases reported in the United States since 1984, which had been in a general slow decline for many years. In the United States, AIDS has been reported in as many as 12% of patients with tuberculosis.

The clinical presentation of tuberculosis in HIV-infected persons varies with the immune status, ranging from the more commonly recognized pulmonary apical cavitation in HIV-infected persons with minimal immune impairment to disseminated disease presenting with blood cultures positive for *M tuberculosis* in persons with advanced AIDS. A 5-mm or more reaction to tuberculin skin testing (purified protein derivative [PPD]) is seen in about a third of those AIDS patients with tuberculosis who are tested. The chest x-ray film often shows an atypical pattern that includes hilar and mediastinal adenopathy. Cavitation is present in less than 25% of cases, and diffuse reticulonodular infiltrations are frequently seen. *M tuberculosis* has been found in the sputum of some AIDS patients with normal chest roentgenograms. Extrapulmonary disease occurs frequently, often associated with pulmonary disease. Although *Mycobacterium avium-intracellulare* is frequently identified in patients with AIDS, acid-fast bacilli identified on staining from any specimen in a high-risk HIV-infected person should be considered and treated as *M tuberculosis* until proved otherwise by culture.

The unusual patterns of tuberculosis in AIDS patients may make diagnosis difficult. Because tuberculosis is both contagious and treatable, every effort should be made to identify *M tuberculosis* in AIDS patients. The PPD skin test remains the most reliable test for detecting tuberculosis infection and should be done as early as possible in any person infected with HIV or diagnosed with AIDS. Any measurable induration should be considered as potentially significant, but a 5-mm or larger reaction is definitely positive. Any abnormality on a chest x-ray film in an AIDS patient should be considered suspicious for tuberculosis. Because of the high frequency of cases of extrapulmonary tuberculosis in patients with AIDS, any body fluid specimen—sputum, bronchial washings, cerebrospinal fluid, pleural fluid, ascitic fluids, urine—or lung biopsy specimen should be processed for acid-fast staining and culture during an evaluation for infection.

Antituberculous medication should be given immediately whenever *M tuberculosis* is found or suspected in persons with HIV infection or at an increased risk for HIV infection. The recommended regimen is isoniazid, 300 mg daily, plus rifampin, 600 mg daily, and pyrazinamide, 1,500 mg daily. Ethambutol at a dose of 25 mg per kilogram of body weight daily should be added to the regimen when central nervous system or disseminated tuberculosis exists or isoniazid resistance is suspected. Pyrazinamide therapy may be discontinued after two months if the sputum smear results have converted to negative. The treatment of documented tuberculosis should be continued for at least 9 to 12 months or until the patient's cultures are negative for *M tuberculosis* at least six months. Tuberculosis in patients with HIV infection or AIDS responds well to antituberculous chemotherapy. When tuberculosis patients with AIDS die, it is usually of other complications of AIDS and not the tuberculosis if they are receiving antituberculous medication.

Preventive therapy should be given to any HIV-infected person or anyone at high risk for infection, regardless of age, who has a positive reaction to a PPD skin test. Actual disease should be excluded before starting the therapy. Preventive therapy in this circumstance consists of giving isoniazid, 300 mg daily, for at least 12 months.

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Opportunities for Preventing Woman Abuse and Battering

WOMAN ABUSE AND BATTERING is a public health problem of epidemic proportions. In a recent national survey, 16% of women reported physical abuse by their spouses; 6% reported severe abuse—that is, punching, kicking, choking, beating, and attacks with a weapon. In 1980 this resulted in 21,000 admissions to hospitals, 99,800 hospital days, 28,700 emergency department visits, 39,900 physician visits, and $44.3 million in medical costs.

Woman abuse is only infrequently identified by physicians. The use of simple nursing protocols with direct questioning has shown that 30% of all women presenting with injuries are battered. Only 10% to 25% of these are diagnosed by emergency department physicians, however. In a recent prospective study of women obtaining private and public prenatal services, 8% reported physical abuse during the current pregnancy and 15% in the past. Prenatal care providers, however, had never asked about abuse.

Early identification and intervention are vital, as violence tends to escalate, and relationship change becomes more

difficult. Physicians from various specialties can play a role in prevention by maintaining a high index of suspicion and asking about abuse in a gentle and supportive way. The following findings, although nonspecific, may be clues to abuse: Obstetrics and gynecology: injury, divorce, separation, or suicide attempt during pregnancy; sexual dysfunction; persistent complaints; abortion, miscarriage, or premature delivery. Medicine or family practice: frequent visits with vague or unremitting symptoms; nonspecific clinical findings; requests for sleep medication or tranquilizers; abuse of drugs (legal or illegal) or alcohol; labels in the medical record such as "hysterical" or "hypochondriac." Emergency medicine: trauma to head, face, breasts, abdomen, or both extremities; history incompatible with injury; previous trauma; coexistence of trauma with complaints of insomnia, anxiety, depression, alcohol or drug abuse; accompaniment by a male partner who is alcoholic, suspicious of medical personnel, or reluctant to leave the patient alone. Pediatrics: women with children having psychosomatic complaints; coexistent child abuse. Psychiatry: anxiety; depression; suicide attempt; alcohol or drug abuse or both, psychosis; an inability to "cope."

Because of the high prevalence of abuse and variable clinical presentation of victims, questioning should be done routinely. It has been shown that women not suffering abuse do not mind being questioned and battered women are grateful that someone has finally asked about abuse. Women should be assessed concerning the potential for lethal violence, offered support, assured that they are not alone, and provided information concerning community resources, such as shelters, counseling programs, and therapeutic programs for abusive men. Because of a ninefold increased risk of suicide, dispensing of pain or psychotropic medications should be minimized. Physicians should maintain frequent contact and remain available to provide support and information as needed. In this way, physicians and other health providers can play a key role in breaking the cycle of violence in American families.

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Editorials

Physicians as Role Models in Society

ROLE MODELS INFLUENCE people of all ages. As we grew up most of us were influenced by role models. Sometimes they were our parents, sometimes our teachers, sometimes athletes. Always, they were persons we admired or who stood for something we admired. Many of us, perhaps more than we remember or realize, have modeled ourselves and our behavior on our role models. As adults, we tend to conform to role models who share our daily lives.

There is something biological about role models. Animals learn how to get food and protect themselves from predators from role models, usually one or both of their parents. Humans have many more role models from which to select, and who these are and what they stand for profoundly affect many of us. Role models for youth may be found in the home, in the schools, on the streets, at the movies, or on television. Traditional role models are undermined when drugs, promiscuous sexual activity, and violence seem to permeate society and cheating and dishonesty are found in respected places. Role models do a great deal to shape society and that for which it stands.

There is much that could be said about role models in the medical profession. Many physicians are fine role models for their colleagues, their patients, and the communities in which they live. To the extent that there is greed, lust for power or prestige, or deviation from personal or ethical standards, the model may become tarnished. And there are many who believe that academic role models in medical schools perform something of a disservice by attracting students into subspecialties of bioscience and technology at the expense of weakening their interest in patients and patient care. But, by and large, physicians stand tall and steadfast and are respected for their personal discipline, their work ethic, and their dedication to patients and health care. They are standing up as best they can to the forces that beset them, and there is mounting evidence that, in any case, they are not about to desert their advocacy of the best care for their patients.

Today's society needs good role models. It may even need physicians as role models, not only for young physicians but for society as a whole. Health now touches almost every facet of society, and physicians have many points of contact with the public. At almost any of these points physicians can be teachers and role models. When physicians finally stopped smoking and took a firm stand, the tide was turned in the war against cigarette smoking. Physicians as role models did help to make a difference.

The medical profession is under stress, to be sure. But when successful under stress, role models, like anyone else, are often most influential and effective. All that is necessary is for physicians to live the reasons for which most entered the profession in the first place—a fascination with bioscience, a desire to help fellow humans needing their professional help, and a wish to use their lives in service to humanity. Living these reasons, which after all is doctoring, and combining this with teaching, which after all is also part of doctoring, can make physicians the very much needed role models in today's very health oriented society.

MSMW

Chronic Urticaria—A Frustrating but Increasingly Understandable Disorder

URTICARIA AND ITS RELATED SYNDROME, angioedema, are extraordinarily common disorders in medical practice, occurring in perhaps as many as 20% of the population at some time during their life. These disorders are also persistent, with many patients having repeated episodes for decades. The lesions are bothersome and mysterious to patients and are frustrating to clinicians. The very ease of their recognition, combined with the difficulty in defining an etiologic diagnosis, has led over the years to a variety of misapprehensions about this disease. Several important caveats need also to be added to any discussion of urticaria. As urticaria is a common disorder, it is not at all unusual for other findings to be noted in patients presenting with it. The conjunction of a common illness with an intercurrent problem does not imply cause and effect. Hence, numerous case reports indicating infection with parasites, occult dental or sinus infection, or other seemingly bizarre or biologically inexplicable associations may be merely the coincident occurrence of two unrelated events. This must always be kept in mind when explanations for urticaria are presented. For example, in one large review, causes of urticaria are listed that most would feel are unproved.[1] Nonetheless, urticaria is so common and is engendered by so many different events that it continues to provide an intellectual and diagnostic challenge to the most astute and persistent clinician. In this issue, Burrall and colleagues provide an up-to-date review of our current clinical understanding of urticaria and its treatment and emphasize our inadequate grasp of the pathobiology of this important syndrome.

Because of the role of histamine in inducing urticaria and the knowledge that histamine is present in the skin almost exclusively in mast cells, it has long been known that mast cells are central to understanding urticaria. Beginning in the early 1970s, it became apparent that various model systems could be used to manipulate cutaneous mast cells and thus tease apart the pathobiology of urticaria. Useful in this regard was, and has been, the model of idiopathic cold urticaria, a disorder that comprises approximately 1% to 2% of cases of chronic urticaria. In patients with this disorder whealing develops on exposure to cold, generally on rewarming of the affected part. This disease may be life-threatening in patients in whom after extensive exposure to cold, such as in bathing or boating accidents, extensive urticaria and angioedema develop, inducing hypotension, which can lead to death by drowning. The ability to activate cold urticaria in the laboratory produced the first model that allowed the obtaining of blood concurrent with lesion development, thereby enabling an analysis of possible molecular causes of urticaria. Histamine, chemoattractant molecules for neutrophils and eosinophils, and platelet-activating factor all have been identified within minutes of the application of cold.[2] In addition, biopsy specimens of the cold-challenged areas reveal mast cell degranulation. As this disorder in a large number of patients can be passively transferred with immunoglobulin (Ig) E antibody, this model system can be linked to that of allergic urticaria. Mast cell activation through IgE antibody and an-

tigen has long been recognized as a cause of acute urticaria, and, in those patients who are unable to avoid the antigen, of chronic urticaria. Rather than pollen antigens, which so commonly cause rhinitis, conjunctivitis, and asthma, the antigens that appear to be most common in the induction of chronic urticaria are foods and other ingestants, such as antibiotics. While food allergy is a highly controversial area and is much more commonly blamed than truly implicated, it is clear that in many patients, ingesting foods is associated with the development of urticaria. Using skin window techniques, it has been found that a variety of mediators are released into the skin on mast cell challenge with antigen in allergic patients.[3] Thus histamine, tryptase, prostaglandin D_2, leukotriene C_4, and platelet-activating factor all can be identified. The similarity of mediators generated by cold and by antigen further solidifies the link between the known IgE mast cell pathophysiology of allergic reactions with that of physical allergy. The potency of the vasoactive mediators generated by mast cells—histamine, leukotriene C_4, prostaglandin D_2, platelet-activating factor, and adenosine—provides a pathophysiologic substrate for inducing urticaria.

More recent developments in mast cell biology and tissue inflammation suggest important mechanisms in addition to IgE-mediated processes whereby mast cell activation may take place and thus urticaria engendered. It has long been recognized that biopsy specimens of urticarial lesions commonly contain infiltrating leukocytes, most particularly mononuclear leukocytes and lymphocytes. Recent work has also shown the dermal deposition of eosinophilic major basic protein at sites of urticaria, suggesting the previous presence of eosinophils and their activation during the development of urticaria (reviewed by Gleich and Adolphson).[4] Infiltrating eosinophils and mononuclear leukocytes can not only generate potent vasoactive mediators (leukotriene C_4, platelet-activating factor) but also release products capable of activating mast cells. Such activators include the eosinophilic major basic protein, neurotoxin, cationic peptide, and peroxidase,[4] and the monocyte products interleukin-1[5] and granulocyte-macrophage colony-stimulating factor.[6] In addition, a large family of molecules termed histamine-releasing factors are generated by monocytes, lymphocytes, and neutrophils.[7] These molecules are capable of activating mast cells and thus causing the release of biologically relevant mast cell mediators. Therefore, mast cell products can be made available to the local microenvironment of the skin and lead to urtication through direct allergen-IgE interactions, through the manipulation of IgE molecules on the surface of the cells through physical means (as in cold urticaria), and also by the participation of a variety of lymphokines, cytokines, and inflammatory cell constituents. This complex situation is further complicated by the knowledge that a number of neuropeptides,[8] including substance P, calcitonin gene-related peptide, vasoactive intestinal polypeptide, and adenosine triphosphate, all of which are present in fine nerve endings, have been shown to be potent degranulators of human cutaneous mast cells. Thus, a variety of signals can lead to urticaria through a similar final common pathway: the mast cell.

Recent advances in mast cell biology have identified two subpopulations of this cell in humans—a mucosal type prominent in gut and peripheral airway, which is dependent on T-lymphocyte growth factors (interleukin-3 and -4),[9] and a connective tissue type found prominently in skin[10] and on serosal surfaces and not directly T-lymphokine regulated. Although all mast cells respond to IgE-mediated signals, the cutaneous mast cell differs from the mucosal type in being extremely sensitive to activation by neuropeptides, but these do not affect the mucosal mast cells. This difference likely underlies the fact that urticaria is so common, appears to be induced by such disparate triggers, and often occurs in the absence of other symptoms felt due to mast cells and their mediators—that is, rhinitis, asthma, conjunctivitis.

The new understanding of mast cell activation has yet to be exploited therapeutically, but recent major advancements have been made in the treatment of urticaria and angioedema. These include the development of new, potent compounds for the treatment of these disorders, particularly new nonsedative antihistaminic compounds. These agents, discussed in the review by Burrall and co-workers, share an inability to cross the blood-brain barrier and, hence, do not interfere with cognition and alertness, while still potently blocking the H_1 receptor. Such drugs have quickly become the mainstay of therapy in urticaria. These new agents have also been supplemented by the discovery that tricyclic antidepressants are extremely potent (if sedating) antihistamines. One of these, doxepin hydrochloride, has also assumed an important place in the treatment of severe, recalcitrant urticaria. It is exciting, however, to contemplate the new pharmacopeia for urticaria as the therapeutic possibilities made available by our new knowledge of mast cell activators are explored.

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Biological Significance of *Giardia*-Specific Antibodies

THE PAST DECADE has been a time of substantial growth in the understanding of immunologic responses against *Giardia lamblia*. The realization that such responses contribute to the clearance of *Giardia* infection came originally from the finding that hypogammaglobulinemia predisposes to chronic giardiasis. Subsequent clinical and experimental studies have generated a relatively coherent picture of *Giardia*-specific

immunity. These studies have included the documentation of human serum antibody responses to *G lamblia,* explorations of intestinal immunity using rodent models of giardiasis, and in vitro work with *Giardia* trophozoites.

In this issue of the journal, Janoff and co-workers report a detailed study of *Giardia*-specific antibody titers in US and Thai populations spanning an age range from infancy to older than 60 years. The most significant finding in this report is that *Giardia*-specific serum IgA persisted at a high level throughout adult life in residents of Thailand but declined after adolescence in the US population studied by the authors. While the reason for this divergence in IgA responses between the two populations is unknown, the authors' data are consistent with the possibility that the persistence of *Giardia*-specific IgA reflects a continual acquisition of *Giardia* from the environment. Thus, *G lamblia* was detected in fecal specimens from young children in Denver and Thailand and from adults in Thailand but not from a population of adults in Denver.

Three important questions are raised by this work. First, because *G lamblia* is an intestinal parasite, is the study of serum antibody responses to this organism a worthwhile exercise? The second issue that calls for comment is whether *Giardia*-specific antibodies contribute to the removal of *G lamblia* from the intestine and, if so, by what mechanism. Finally, do *Giardia*-specific antibodies help to protect a person against *G lamblia* infection?

The presence of anti-*Giardia* antibodies in human serum has been extensively documented.[1] In contrast, little is known about the presence or absence of such antibodies in human intestinal secretions. That *G lamblia*-infected persons mount an intestinal antibody response to the parasite has, however, been shown in one experimental study. In this work, human volunteers were inoculated with viable *G lamblia* trophozoites—introduced into the lumen of the small intestine through a peroral tube—and trophozoite-specific IgA was detected in jejunal fluid subsequently obtained from these subjects.[1]

Most of the available information about *Giardia*-specific intestinal immunity has been obtained by studying mice infected with *Giardia muris,* a rodent parasite that closely resembles *G lamblia.* Like *G lamblia*-infected human subjects, mice that are infected with *G muris* generate a trophozoite-specific intestinal IgA response. Another point of similarity with human giardiasis is that *G muris* infection leads to the appearance of trophozoite-specific IgG and IgA in the serum of infected mice (M.F.H., unpublished observations, April 1989).[2] Intestinal IgA from *G muris*-infected mice (but not from uninfected mice) binds to trophozoite surfaces in vitro, suggesting that this IgA is directed against one or more surface antigens of the parasite (M.F.H. and J. Pappo, "Recognition of a 30-Kilodalton Antigen of *Giardia muris* Trophozoites by Intestinal IgA From *Giardia*-Infected Mice," unpublished manuscript). An earlier suggestion that mice can generate an intestinal IgG response to *G muris* has not been confirmed by recent work, and current evidence indicates that mouse intestinal *Giardia*-specific antibody consists largely, or exclusively, of IgA.

What is known about the trophozoite antigens that are recognized by human or rodent *Giardia*-specific antibodies in vivo? This is an area of research activity that promises to generate important clues about the mechanisms of protective immunity against *Giardia* infections. As would be expected, *Giardia* trophozoites contain numerous proteins, any one of which might theoretically generate a host antibody response. It is, therefore, of great interest that the antibodies that develop in response to *Giardia* infection appear to be directed against a limited number of parasite proteins. Much of the "action" involves a group of trophozoite proteins that have a molecular weight of approximately 30,000. Western blotting and immunoprecipitation studies have shown that trophozoite proteins of this molecular weight are recognized by serum antibodies from *Giardia*-infected human subjects and mice.[3,4] Furthermore, intestinal IgA from *G muris*-infected mice reacts with one or more trophozoite proteins of a molecular weight of about 30,000 (M.F.H., J. Pappo, "Recognition of a 30-Kilodalton Antigen of *Giardia muris* Trophozoites by Intestinal IgA From *Giardia*-Infected Mice," unpublished manuscript). Collectively, these recent studies suggest that the immunodominant antigens of *G lamblia* (in humans) and of *G muris* (in mice) have a similar molecular weight and that mouse serum and intestinal *Giardia*-specific antibodies may recognize the same antigen of the parasite.

It has been known for many years that *Giardia* trophozoites attach to the intestinal epithelium by means of an adhesive disk located on their ventral surfaces. The ability of trophozoites to adhere in this way is thought to help them to remain in the small intestinal lumen, instead of being expelled by peristalsis. What has emerged from recent studies is the finding that trophozoites may also adhere by a chemical mechanism involving the interaction between a protein expressed on their surfaces and carbohydrate groups protruding from epithelial cells.[5] The trophozoite molecule involved in this linkage is an example of a lectin, a carbohydrate-binding protein. Intriguingly, the lectin on *G lamblia* trophozoites has a molecular weight of approximately 30,000.[5] It is tempting to speculate that this molecule is recognized by trophozoite-specific antibody in the intestinal lumen; the similarity in molecular weight of the lectin and of trophozoite immunodominant antigens is striking.

The binding of intestinal antibody to the surface lectin of *Giardia* trophozoites would be expected to inhibit their attachment to epithelial cells of the host intestine. Is there any evidence that *Giardia*-specific antibody can actually inhibit such attachment? An affirmative answer to this question has been provided by one recent study in which the attachment of *G lamblia* to intestinal epithelial cells was found to be inhibited by trophozoite-specific antibodies.[6] Other recent work has examined the possible ability of *Giardia*-specific antibodies to cure or prevent *Giardia* infections. Administering such antibodies to *Giardia*-infected rodents (by intraperitoneal injection or directly into the duodenal lumen) has been shown to diminish the intensity of *Giardia* infections, as judged by a reduction in numbers of intestinal trophozoites or fecal *Giardia* cysts.[7] Along similar lines, the ability of *G muris* trophozoites to infect mice is reduced by incubating the trophozoites with *Giardia*-specific antibody in vitro.[8] These experimental studies leave little doubt that, at least in rodents, antibodies contribute to the clearance of *Giardia* infections and help to protect against colonization of the intestine by *Giardia* trophozoites.

It is theoretically possible that *Giardia* trophozoites might be killed by antibody in the host intestine. An experimental study has shown that *G muris* trophozoites are killed, in the

presence of complement, by serum antibody from *Giardia*-immunized rabbits.[9] There is no evidence, however, that *Giardia*-specific intestinal IgA can kill trophozoites (M.F.H., unpublished observations, September 1989). In summary, the most likely way in which intestinal antibody contributes to the clearance of *Giardia* infections is by inhibiting trophozoite attachment to the intestinal epithelium.

Does cell-mediated immunity play any part in the host response to *Giardia* infections? In asking this question, the meaning of "cell-mediated" needs to be clearly understood—that is, the direct killing of *Giardia* trophozoites by macrophages or by lymphocytes acting as cytotoxic effector cells (as opposed to helper cells for antibody production by B lymphocytes). Summarizing the results of various studies, it can be confidently stated that cytotoxic lymphocytes (natural killer cells and $CD8^+$ T lymphocytes) play no discernible role in the clearance of *Giardia* infections. Similarly, there is no convincing evidence that macrophages ingest or kill trophozoites in the intestinal lumen of *Giardia*-infected hosts. Macrophages may, however, initiate antibody responses to *Giardia* trophozoites by presenting trophozoite antigens to lymphocytes in Peyer's patches of the small intestine. Furthermore, the ability of immunocompetent mice to clear *G muris* infection is dependent on the presence of $CD4^+$ (helper) T lymphocytes. *Giardia muris*-infected mice that have been depleted of $CD4^+$ T lymphocytes (by treatment with anti-CD4 monoclonal antibody) do not mount an intestinal IgA response to the parasite or clear the infection.[10]

Can human giardiasis be confidently diagnosed, or excluded from diagnostic consideration, by demonstrating the presence or absence of *Giardia*-specific antibodies in a person's serum? The answer to this question, based on data available in the literature, appears to be no.[11] Perhaps the most that can be said about the diagnostic usefulness of *Giardia*-specific antibodies is that they commonly indicate a previous *G lamblia* infection.[1]

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Case Reports

Tropical Pyomyositis of the Abdominal Wall Musculature Mimicking Acute Abdomen

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FIRST DESCRIBED by Scriba in 1885, tropical pyomyositis is a necrotizing infection of skeletal muscle.[1] A common disorder in equatorial zones, tropical pyomyositis accounts for as much as 4% of surgical admissions in certain regions of Africa, Southeast Asia, and the South Pacific.[2] Although historically uncommon in the continental United States, the first cases were reported by Levin and co-workers in 1971 in three patients who had recently immigrated from India, Puerto Rico, and Biafra.[3] Most cases have a subacute presentation with muscle pain as the dominant early manifestation. Overlying erythema and tactile warmth, followed by edema and eventual fluctuance, occur late in the course of the disease. Secondary bacteremia with metastatic abscess formation is an infrequent but well-recognized complication. A delay in diagnosis occurs commonly as overt inflammatory signs are often absent. *Staphylococcus aureus* is the dominant pathogen and accounts for more than 95% of cases. Recent reports have implicated *Streptococcus pneumoniae*, group G streptococci, *Neisseria gonorrheae, Yersinia enterocolitica, Klebsiella pneumoniae,* and *Aeromonas hydrophila* as pathogens capable of causing pyomyositis.[4-9] Noninvasive imaging with ultrasonography or computed tomography will locate the abscess in most cases.[10,11] Percutaneous needle aspiration will provide adequate material for a microbiologic diagnosis, but incision and drainage combined with parenteral antibiotics remain the standard of management. With this report we would add abdominal wall tropical pyomyositis to the differential diagnosis in patients presenting with symptoms and physical findings indicative of an acute abdominal process.

Report of a Case

The patient, a 19-year-old man, presented to the emergency department with abdominal pain and fever of three weeks' duration. Night sweats and weight loss of 7.3 kg (16 lb) occurred during the month preceding evaluation. Intermittent right lower quadrant pain that was stabbing in character and worsened by defecation, coupled with nausea and intractable vomiting, prompted an emergency evaluation.

The patient had immigrated to the United States from El Salvador ten months before being seen. His medical history was remarkable only for malaria and intestinal parasitosis. He admitted to infrequent melena over a five-year period but said he did not have a history of inflammatory bowel disease, ethanol abuse, peptic ulcer disease, or the use of aspirin or nonsteroidal anti-inflammatory agents. He specifically said he had never had blunt abdominal trauma. No previous episodes of soft tissue or visceral infection had occurred, and the patient adamantly denied intravenous drug use.

On physical examination he was thin and appeared ill and in acute distress. The temperature was 39.6°C (103.2°F), the blood pressure 110/70 mm of mercury, with a pulse rate of 106 in the supine position. On standing his blood pressure fell to 70/50 mm of mercury, with a pulse rise to 134 beats per minute. Respirations were 18 per minute and unlabored. The sclerae were anicteric, and conjunctival injection was absent. The jugular venous pressure was reduced and the carotid pulsations hyperdynamic. The oropharynx was parched. Splinting of the right hemithorax was noted with inspiration, and breath sounds in the right lung base were diminished. A grade 2/6 systolic murmur was heard across the precordium. The abdomen was firm and bowel tones infrequent. Hepatosplenomegaly was not detected. Rebound tenderness and guarding were pronounced in the periumbilical and right lower quadrant zones. The rectal examination was remarkable for Hemoccult-positive stool. Increased tactile warmth was present in the right hemiabdomen without soft tissue swelling, erythema, or fluctuance.

Electrolytes, blood urea nitrogen level, and the serum creatinine value were normal. The hematocrit was 0.44, the platelet count 292×10^9 per liter, and the leukocyte count 15.2×10^9 per liter with 0.71 segmented neutrophils, 0.18 band forms, and 0.06 eosinophils. Liver function studies revealed a bilirubin level of 26 μmol per liter, alkaline phosphatase of 135 units per liter, and normal aminotransferase levels. The serum amylase level was 774 nmol per liter, and a routine analysis of urine showed no abnormalities. Plain and upright abdominal radiographs failed to show intraperitoneal air or evidence of bowel obstruction. Abdominal ultrasonography showed a homogeneous liver without biliary duct dilatation. The appendix was visualized, and no abnormalities suggestive of a periappendiceal abscess were detected. Blood specimens for culture were obtained, intravenous access established, and a regimen of a combination drug, ampicillin sodium and sulbactam sodium, with gentamicin sulfate was begun for presumed intra-abdominal sepsis. Computed tomography of the abdomen revealed no parenchymal abnormalities in the liver, spleen, pancreas, or kidneys. The right rectus abdominis and oblique musculature was notably edematous. Multiple hypodense abscess cavities were present deep in the abdominal wall musculature without overlying soft tissue swelling (Figure 1). Needle aspiration yielded overt pus, and a Gram's stain showed copious gram-positive cocci in clusters with polymorphonuclear granulocytes. The ampicillin-sulbactam therapy was discontinued and nafcillin sodium substituted. A surgical consultation was

(Kennedy CA, Mathisen G, Goetz MB: Tropical pyomyositis of the abdominal wall musculature mimicking acute abdomen. West J Med 1990 Mar; 152:296-298)

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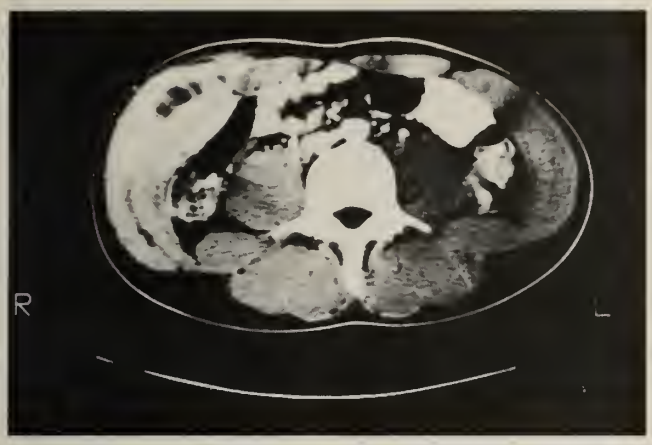

Figure 1.—A computed tomographic scan of the abdomen shows pronounced edema and multiple septate, hypolucent abscess cavities within the right internal oblique, external oblique, and rectus abdominis muscles. Note the absence of soft tissue swelling overlying the area of pyomyositis.

done and incision and drainage carried out. Cultures of specimens obtained at the time of needle aspiration grew *Staphylococcus aureus* sensitive to methicillin, vancomycin, erythromycin, cefazolin, clindamycin, and gentamicin. The organism was resistant to penicillin, ampicillin, tetracycline, and trimethoprim-sulfamethoxazole. Cultures of three sets of blood specimens drawn in the emergency department were negative for pathogens. Defervescence was rapid, and the abdominal wound was allowed to heal by secondary intention. Ova and parasite examination of the stool revealed eggs of *Ancylostoma duodenale,* and Hemoccult-positivity resolved after a short course of oral mebendazole. The patient completed a 14-day regimen of intravenous antibiotics followed by 1 week of oral dicloxacillin sodium. On follow-up examination, the wound was entirely healed and no residual tenderness was present.

Discussion

Tropical pyomyositis, a suppurative infection of striated muscle, was first reported by Scriba in 1885.[1] Called "tropical" because of its prevalence in equatorial regions of Africa, Asia, and the Caribbean, pyomyositis has rarely been reported in the continental United States. Levin and associates in 1971 described three cases of staphylococcal pyomyositis in patients who had recently immigrated to America from India, Puerto Rico, and Biafra.[3] Since the original description fewer than 50 cases have been reported in the United States. *Staphylococcus aureus* accounts for 95% of reported cases. More recently *Streptococcus pneumoniae,* group G streptococci, *Neisseria gonorrheae, Yersinia enterocolitica,* and *Aeromonas hydrophila* have been reported as pathogens capable of causing pyomyositis.[4-9]

Tropical pyomyositis occurs more frequently in men than in women. Blunt trauma to large muscle groups, without disruption of the overlying soft tissue, is reported in a substantial percentage of patients and may explain the male predominance of this disease. More cases of tropical pyomyositis are seen during the summer and early fall months than at other times of the year. Most patients with pyomyositis lack serious underlying disease, but this disorder has been reported in a variety of immunocompromised states including diabetes mellitus, granulocytic and lymphocytic leukemias, aplastic anemia, and, most recently, in progressive systemic sclerosis and the acquired immunodeficiency syndrome.[5,12-16] We have seen three patients with the acquired immunodeficiency syndrome and staphylococcal pyomyositis (manuscript in preparation). Murphy and colleagues have recently reported delayed intracellular killing of *S aureus,* despite increased levels of superoxide anion, in neutrophils of patients infected with the human immunodeficiency virus.[17]

Tropical pyomyositis predominantly involves large muscle groups of the upper and lower extremities. The axial musculature is infrequently involved. Most patients have a single abscess, but multiple abscess cavities occur in as many as 40% of cases. Chiedozi, in a series of 112 patients from Nigeria with pyomyositis, described involvement of the paravertebral and gluteal musculature in 43 patients, but no abscesses occurred in the rectus abdominis or oblique groups.[18] Brown and Wheeler reported 18 cases of tropical pyomyositis from Hawaii, and no patients in their series had abdominal wall involvement.[19] In the pediatric literature, Beck and Grose in 1984 reported the cases of two children with tropical pyomyositis of the abdominal wall musculature.[20] To our knowledge, after extensive review of the literature, this is the first case of abdominal wall pyomyositis in an adult reported in the United States.

Many patients describe antecedent, nonpenetrating trauma before the development of staphylococcal pyomyositis. Ashken and Cotton in 1963 reported a series of pyomyositis cases in military recruits, two thirds of whom had experienced previous trauma.[21] In 12 of 18 patients described by Brown and Wheeler, previous trauma to muscle was reported; in some patients, however, the traumatized area was not in the anatomic distribution where pyomyositis subsequently developed.[19] Many have postulated that hematoma formation is a prerequisite for the development of pyomyositis, which provides a nutrient-rich focus for bacteremic seeding. Of interest, in established cases of pyomyositis, bacteremia is distinctly uncommon and is documented in less than 5% of patients.[18] As early as 1904, Miyake was unsuccessful in his attempt to develop an animal model of tropical pyomyositis by simply inducing staphylococcal bacteremia. After crush injury, however, ligation of a vascular supply, or the application of electrical shock, staphylococcal bacteremia easily induced pyomyositis in damaged muscle groups.[22]

Pyomyositis has been divided into three distinct phases characterized by clinical manifestations. In stage I, pain in the affected muscle group predominates, with fever and diffuse myalgias being common associated symptoms. Early in the course of pyomyositis, leukocytosis with a left shift and an elevated erythrocyte sedimentation rate are found. Diagnostic imaging at this stage rarely reveals a discrete abscess, and needle aspiration does not yield purulent material. Stage II occurs 10 to 21 days after the beginning of symptoms and is characterized by pronounced fever, localized pain, muscle edema, and overlying erythema and induration. Aspiration during the second phase yields polymorphonuclear granulocytes, and organisms are easily identified on Gram's stain. Despite extensive muscle necrosis, elevations of the creatine kinase and aldolase levels virtually never occur. Secondary bacteremia may occur in stage III of the disease with the formation of metastatic abscesses. Pneumonia, purulent

pericarditis, septic arthritis, and a toxic shock-like syndrome have been reported as secondary manifestations of tropical pyomyositis.[18,19,23]

Of interest, our patient had fecal occult blood, and microscopic examination of the stool revealed eggs of *Ancylostoma duodenale*. Some authors have postulated underlying parasitic infection as a possible predisposing factor in tropical pyomyositis. In the largest published series of 112 patients, no data are provided regarding concomitant parasitic infection. In this cohort of patients from Nigeria, eosinophilia was common and it is safe to assume that coexisting parasitic infection was prevalent. A causal relationship between parasitic infection and tropical pyomyositis has not been definitively proved, and it is likely that this association reflects the endemic prevalence of two commonly occurring diseases. Furthermore, Taylor and co-workers have suggested, on the basis of histopathologic studies and electron microscopy, that antecedent Coxsackie virus infection may predispose to the development of staphylococcal pyomyositis.[24,25]

Our patient presented with fever, abdominal pain, and localizing peritoneal signs. Leukocytosis with bandemia, tachycardia, and postural hypotension were present. The findings of a physical examination strongly suggested an acute abdomen. Of note was the lack of erythema or induration in the area of guarding and rebound tenderness. Abdominal ultrasonography failed to show a recognizable focus of intra-abdominal infection. Despite previous reports describing the usefulness of ultrasonography in localizing pyomyositis, the abscess cavities were completely overlooked in this case.[10,11] Computed tomography revealed massive edema and multiple abscess cavities within the rectus abdominis and oblique musculature. Infection of the abdominal wall musculature directly overlying the peritoneum produces physical findings that are indistinguishable from those of an acute abdomen. Despite localizing abdominal findings, the septic focus in our patient was entirely extraperitoneal. During surgical drainage, the muscle was found to be infected through its full thickness and peritoneal hyperemia was noted without evidence of intra-abdominal communication.

No data exist on the appropriate duration of therapy for tropical pyomyositis. Likewise, no clinical trials have been published comparing the efficacy of various antibiotic regimens. In cases of possible tropical pyomyositis, empiric antibiotic therapy should consist of a semisynthetic penicillin or first-generation cephalosporin in combination with gentamicin, as *S aureus* is epidemiologically the most likely pathogen. While historical data suggest that some cases of tropical pyomyositis may resolve spontaneously, surgical drainage and parenteral antibiotic administration for a two- to three-week period remain the standard of care and protect against secondary infectious complications.

Acute appendicitis, periappendiceal abscess, ileocecal tuberculosis, inflammatory bowel disease, and hepatitis were diagnostic considerations in our patient. Plain radiographs and ultrasonography were unhelpful. Computed tomography of the abdomen followed by needle aspiration yielded the correct diagnosis. Open surgical drainage and antistaphylococcal therapy resulted in complete resolution.

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Successful Medical Treatment of Listerial Brain Abscess

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Listeria monocytogenes is a gram-positive bacillus that can be differentiated from other gram-positive bacilli by its motility at room temperature and its hemolysis of blood agar. It is well recognized as an opportunistic pathogen.[1,2] *Listeria* is known to have a predilection for neural tissue, but listerial brain abscesses occur rarely.[1,3] The necessity for surgical abscess drainage, the choice of antibiotic regimen, and the optimal duration of therapy are unresolved issues. We report

(Updike WS, Anderson CJ, Lundberg MS, et al: Successful medical treatment of listerial brain abscess. West J Med 1990 Mar; 152:298-301)

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ABBREVIATIONS USED IN TEXT

CSF = cerebrospinal fluid
CT = computed tomography

the case of a patient who recovered from listerial brain abscesses with a regimen of intravenous and oral ampicillin, without surgical drainage.

Report of a Case

The patient, a 60-year-old woman with a seven-year history of rheumatoid arthritis, had digital vasculitis develop in the fall of 1985, which progressed to cause gangrenous changes in several digits in both hands and feet despite high-dose corticosteroid therapy. Cyclophosphamide was added to her therapy in January 1986, but its use was discontinued after two months because of anemia and hypoplastic bone marrow changes on biopsy. She continued to receive 60 mg of prednisone daily. Serum aminotransferase concentrations became elevated over the next two months, and, in mid-May 1986, the patient was admitted for liver biopsy. Except for fatty infiltration, the liver biopsy findings were unremarkable. Over the next two weeks she became progressively lethargic, weak, and confused. She said she did not have fever, chills, headache, or neck stiffness. She was readmitted for further evaluation.

On general examination she was cushingoid and appeared mildly confused. Her temperature was 36.8°C (98.6°F); blood pressure, 174/110 mm of mercury; pulse, 120 beats per minute; and respirations were 20 per minute. A funduscopic examination revealed normal optic disks. Her neck was supple. The lung fields were clear. She had a grade 2/6 systolic murmur at the left lower sternal border. Dry gangrene was noted in the distal portions of several fingers on both hands and in three toes of the right foot. The lesions did not appear to be infected. The patient was oriented to person, place, and time but responded slowly to questions. Examination of the cranial nerves, muscle strength, sensation, deep tendon reflexes, and cerebellar function elicited no abnormalities.

The leukocyte count was 10.2×10^9 per liter (10,200 per μl), with 0.74 polymorphonuclear cells, 0.04 bands, and 0.15 lymphocytes. Serum electrolyte concentrations were as follows: sodium, 118 mmol per liter; chloride, 76 mmol per liter; potassium, 4.6 mmol per liter; and carbon dioxide, 13 mmol per liter. The cerebrospinal fluid (CSF) contained only 1×10^6 per liter leukocyte (1 per μl), with 1.00 lymphocytes on the differential cell count. The CSF protein level was 1.02 grams per liter (102 mg per dl), glucose 16.5 mmol per liter (298 mg per dl), and lactate 7.1 mmol per liter. Cultures of the CSF specimen grew no pathogens.

Shortly after the lumbar puncture was done, the patient suffered a generalized tonic-clonic seizure. A contrast-enhanced computed tomographic (CT) scan of the head revealed two ring-enhancing lesions in the right cerebrum (Figure 1). A regimen of nafcillin, 2 grams every four hours, and gentamicin sulfate, 1 mg per kg of body weight every eight hours, was administered intravenously. The following day the patient underwent stereotaxic needle aspiration of the two cerebral abscesses. *Listeria monocytogenes* was cultured from the fluid obtained from both sites and from the blood. The patient received intravenous ampicillin in a dose of 2 grams every four hours for the next eight weeks. Her clinical condition improved on this therapy, and the size of the abscesses decreased on CT scan. She was discharged at the end of eight weeks on a regimen of amoxicillin, 1 gram, and probenecid, 1 gram orally, given in combination four times a day. Her prednisone dose was tapered during the hospital stay to 30 mg daily, and she remained on that dose. Computed tomographic scans obtained at two- to three-month intervals showed a gradual resolution of the abscesses. After 24 months of therapy, there was no radiographic evidence of the abscesses, and antibiotic therapy was stopped (Figure 2). She has currently been off antibiotic therapy for eight months without recurrent infection and is without neurologic sequelae.

Discussion

Among 186 cases of listeriosis reviewed in 1978 by Nieman and Lorber, 102 patients (55%) had meningitis and 2 (1%) had brain abscesses.[1] In 1986, Dee and Lorber reviewed 14 cases of listerial brain abscess and concluded that surgical intervention is indicated for establishing the diagnosis and treatment in the presence of a mass effect.[3]

The clinical characteristics of our patient and all previously reported patients with listerial brain abscess are recorded in Table 1.[2,4-15] This case was unusual in several respects. The patient was afebrile at presentation, and her infection first manifested with seizures. Of the 14 patients in the Dee and Lorber review, 1 was afebrile at presentation, and only 2 others of the reported cases had seizures as a presenting sign. Our patient recovered completely without surgical drainage of the abscesses or the cessation of immunosuppressive therapy. Of previous cases reported with

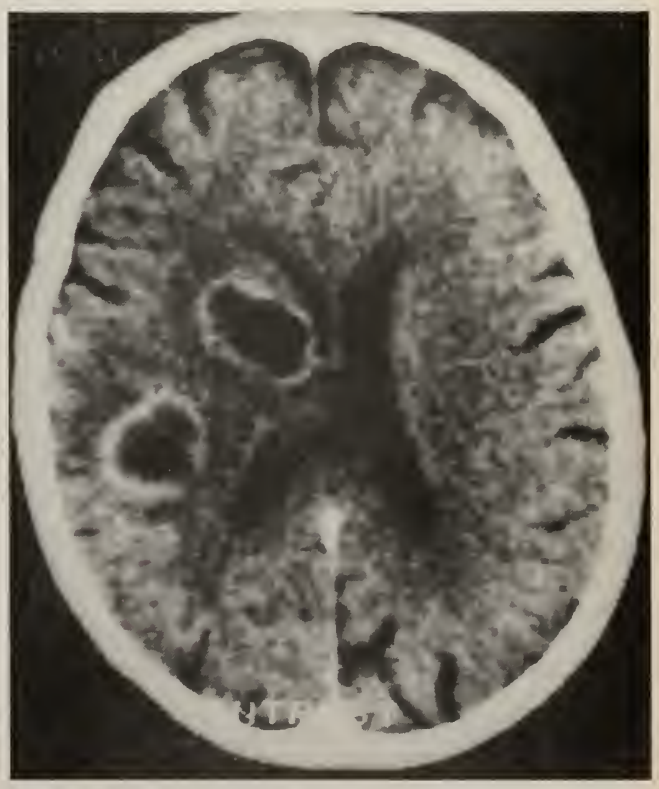

Figure 1.—A computed tomographic scan of the head with contrast enhancement shows two ring-enhancing lesions in the right cerebrum.

treatment details (11 of 14 cases), four of four patients (100%) who underwent surgical drainage survived, whereas two of six (33%) who were treated with antibiotics only survived.

The difference between successful and unsuccessful antibiotic regimens in patients treated with antibiotics alone is not apparent. The two reported survivors received ampicillin or penicillin and chloramphenicol. Our patient received ampicillin alone after initial treatment with nafcillin and gentamicin for 36 hours. Of the four patients who died, one received penicillin and chloramphenicol, one received penicillin alone, and two received chloramphenicol alone. In vitro, *L monocytogenes* is sensitive to the β-lactam antibiotics, erythromycin, chloramphenicol, tetracycline, and rifampin, but these agents are bacteriostatic. Only the aminoglycosides and the combination of trimethoprim and sulfamethoxazole are bactericidal against *Listeria* species, and effective CSF levels of aminoglycosides are usually not achievable. A synergy between ampicillin and gentamicin has been shown in vitro. Trimethoprim-sulfamethoxazole has good central nervous system penetration and has been used successfully to treat listerial meningitis.[16] There are no published reports, however, of cases of listerial brain abscess treated with trimethoprim-sulfamethoxazole. Based on a review of clinically effective antibiotic regimens for listeriosis and in vitro studies, Dee and Lorber recommended a four- to six-week regimen of ampicillin and gentamicin.[3]

One factor that contributed to the four deaths in the group of patients who received antibiotics alone may have been the

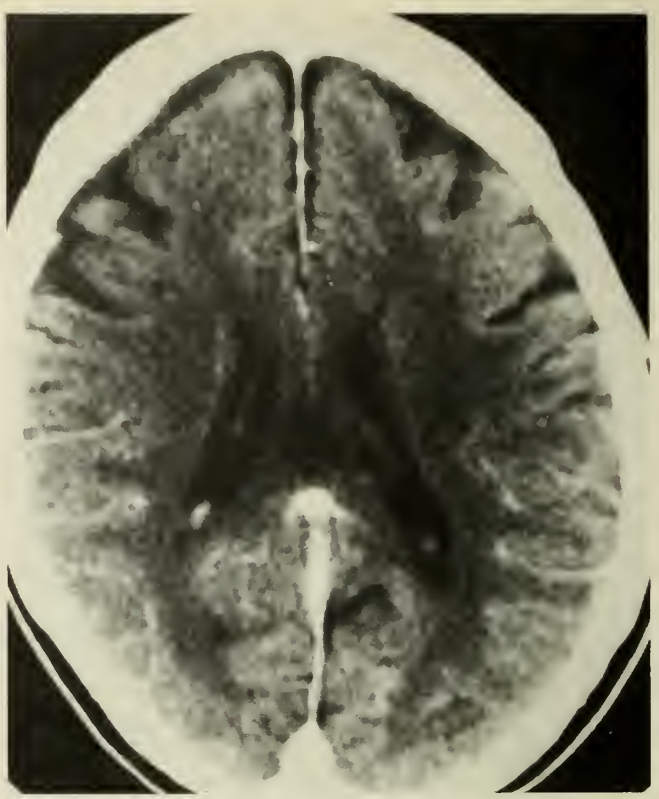

Figure 2.—A computed tomographic scan of the head with contrast enhancement after 24 months of antibiotic therapy shows resolution of the abscesses.

TABLE 1.—*Summary of Published Reports of Patients With Listerial Brain Abscess*

Case	Procedures	Diagnostic Cultures	Diagnosis of Brain Abscess	Antibiotics	Surgery	Immuno-suppression	Outcome	Source
1	None	Blood, CSF, postmortem	Postmortem	Penicillin, chloramphenicol	No	No	Died	Spilkin et al, 1968[4]
2	EEG, carotid angiogram, pneumoencephalogram	Blood	Postmortem	Penicillin	No	No	Died	Buchner and Schneierson, 1968[5]
3	None	Postmortem unspecified	Postmortem	NR	No	NR	Died	Editor, 1971[6]
4	EEG, carotid angiogram	Blood	At surgery	Penicillin, erythromycin PO	Yes	NR	Survived	Halkin et al, 1971[7]
5	Carotid angiogram, brain scan	Blood, CSF	Postmortem	Chloramphenicol	No	Yes, azathioprine, prednisone	Died	Crocker and Leicester, 1976[8]
6	None	Postmortem unspecified	Postmortem	Chloramphenicol PO	No	Yes, leukemia	Died	Larsson et al, 1978[9]
7	CT scan, carotid angiogram, brain scan	Blood	CT	Ampicillin	Yes	Yes, azathioprine, prednisone	Survived	Lectenberg et al, 1979[10]
8	CT scan	Blood, CSF	CT	Penicillin, chloramphenicol	No	No	Survived	Dykes et al, 1979[11]
9	NR	NR	NR	NR	No	No	Died	Larsson and Linell, 1979[12]
10	NR	NR	NR	NR	No	No	Died	Larsson and Linell, 1979[12]
11	CT scan	Blood	CT	Ampicillin	Yes	Yes, azathioprine, prednisone	Survived	Stam et al, 1982[13]
12	CT scan	Blood, CSF	CT	Ampicillin plus chloramphenicol or gentamicin or erythromycin PO	No	Discontinued at time of diagnosis	Survived	Hutchinson and Heyn, 1983[14]
13	NR	NR	Postmortem	NR	No	NR	NR	Pollock et al, 1984[15]
14	CT scan	Abscess	CT, drainage	Ampicillin, gentamicin	Yes	Discontinued at time of abscess drainage	Survived	Louria et al, 1967[2]
15	CT scan	Blood, abscess	CT, biopsy	Ampicillin	No	Yes, prednisone	Survived	This case

CSF=cerebrospinal fluid, CT=computed tomography, EEG=electroencephalogram, NR=not recorded, PO=by mouth

delay in the diagnosis of brain abscess. All four cases occurred before 1974, and none of the patients received CT scans. The two surviving patients in the antibiotic-only group were evaluated with CT scans at the time of presentation and serially, as was our patient. The contribution of computed tomography to the successful treatment of bacterial brain abscesses was noted in a retrospective analysis of patients treated at the University of California, San Francisco, from 1970 through 1977.[17] The mortality rate before 1974, when computed tomography became available at that hospital, was 44% (8 of 18). In contrast, there were no deaths in the 20 patients diagnosed after the CT scan became available.

In summary, a review of reported cases of listerial brain abscess suggests that, like other forms of bacterial brain abscess, the chance of cure is increased by abscess drainage. Because our patient underwent only needle aspiration of her abscesses and received only four doses of gentamicin, which is known to have poor central nervous system penetration, we think this case shows that a cure of listerial brain abscess is possible without surgical abscess drainage or the use of a nephrotoxic antibiotic even in a patient receiving immunosuppressive medication.

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Association of Spontaneous Pneumomediastinum With Substance Abuse

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THE SPONTANEOUS OCCURRENCE of air in the mediastinum is well described.[1,2] Usually a benign condition, it can be indistinguishable clinically from potentially life-threatening causes of pneumomediastinum such as esophageal perforation.[3] Isolated cases of pneumomediastinum have been reported following the inhalation of marijuana[4,5] and cocaine use.[5-7] We present four cases of adolescents who had pneumomediastinum after inhaling marijuana or alkaloidal cocaine. In all four, recovery was uneventful.

Report of Cases

Case 1

The patient, a 17-year-old previously healthy male adolescent, was admitted to hospital from the emergency department because he had had acute retrosternal chest pain for six hours that radiated to the neck. There was no history of reactive airways disease, recent trauma, dyspnea, hemoptysis, or tobacco abuse.

On physical examination, the patient was in pain and anxious but in no respiratory distress. Breath sounds and the findings of a cardiac examination were normal. No Hamman's sign was present. Laboratory data revealed normal arterial blood gas measurements while the patient was breathing room air (pH 7.42, Po_2 96 mm of mercury, Pco_2 35 mm of mercury). A posteroanterior chest radiograph was relatively unremarkable, but the lateral view showed lucency

Figure 1.—A lateral chest radiograph shows pneumomediastinum with air lucency in the pretracheal space **(arrows)** and surrounding the right pulmonary artery **(arrowheads).**

(Fajardo LL: Association of spontaneous pneumomediastinum with substance abuse. West J Med 1990 Mar; 152:301-304)

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anterior and posterior to the trachea and circumferentially around the left pulmonary artery (Figure 1).

On further questioning, the patient admitted to several hours of inhaling alkaloidal cocaine before the chest pain began. Clinical symptoms spontaneously regressed over the next two days, and the patient was discharged after 48 hours of observation. A second chest radiograph taken before discharge showed a decrease in the amount of mediastinal air, and a chest film was normal three days after discharge.

Case 2

The patient, a 20-year-old man, presented with shortness of breath and burning substernal chest pain that radiated through his back and up into both sides of his neck. The symptoms occurred about an hour after the patient "free-based" cocaine. In addition, he reported a blow to the midsternal area of the chest on the evening before admission while play boxing. The patient had had pulmonary coccidioidomycosis at the age of 10.

On physical examination there was a pericardial friction rub at the third and fourth intercostal spaces in the midclavicular line and tenderness to palpation over the midsternum and along the right and left paratracheal areas. A chest radiograph showed pneumomediastinum with dissection of air into the subcutaneous tissues of the neck (Figure 2). A laboratory workup elicited no abnormalities.

The patient was observed overnight in the hospital. The findings of a chest film taken 14 hours after admission were unchanged, but his symptoms were resolving. He was discharged from the hospital and followed up in the outpatient clinic. Four days after discharge the patient was asymptomatic and his chest radiograph was normal.

Case 3

A 19-year-old man awoke with a sore throat and substernal aching that worsened with inspiration. On physical examination there was a positive Hamman's sign. Chest radiography showed a subtle pneumomediastinum and dissection of free air superiorly into the soft tissues of the neck (Figure 3). A barium esophagogram was normal. The patient later revealed that he had smoked marijuana the evening before his symptoms occurred. The patient's chest radiograph findings were unchanged 24 hours after admission, but his symptoms had resolved and he was discharged. He did not keep his follow-up outpatient appointment.

Case 4

The patient, a 16-year-old male adolescent, was transferred from an emergency department in Mexico with pneumomediastinum and chest pain. The patient was well until

Figure 2.—An anteroposterior chest radiograph shows pneumomediastinum **(arrowheads)** with dissection of air into the subcutaneous tissue planes of the neck **(arrows)**.

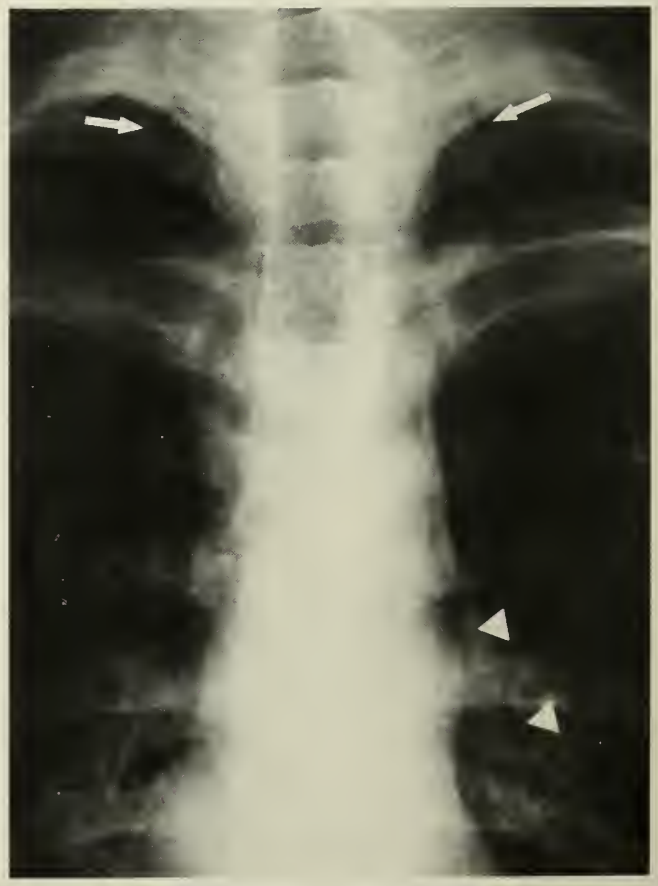

Figure 3.—An anterolateral chest radiograph shows pneumomediastinum **(arrowheads)** and dissection of air into the subcutaneous tissues of the neck **(arrows)**.

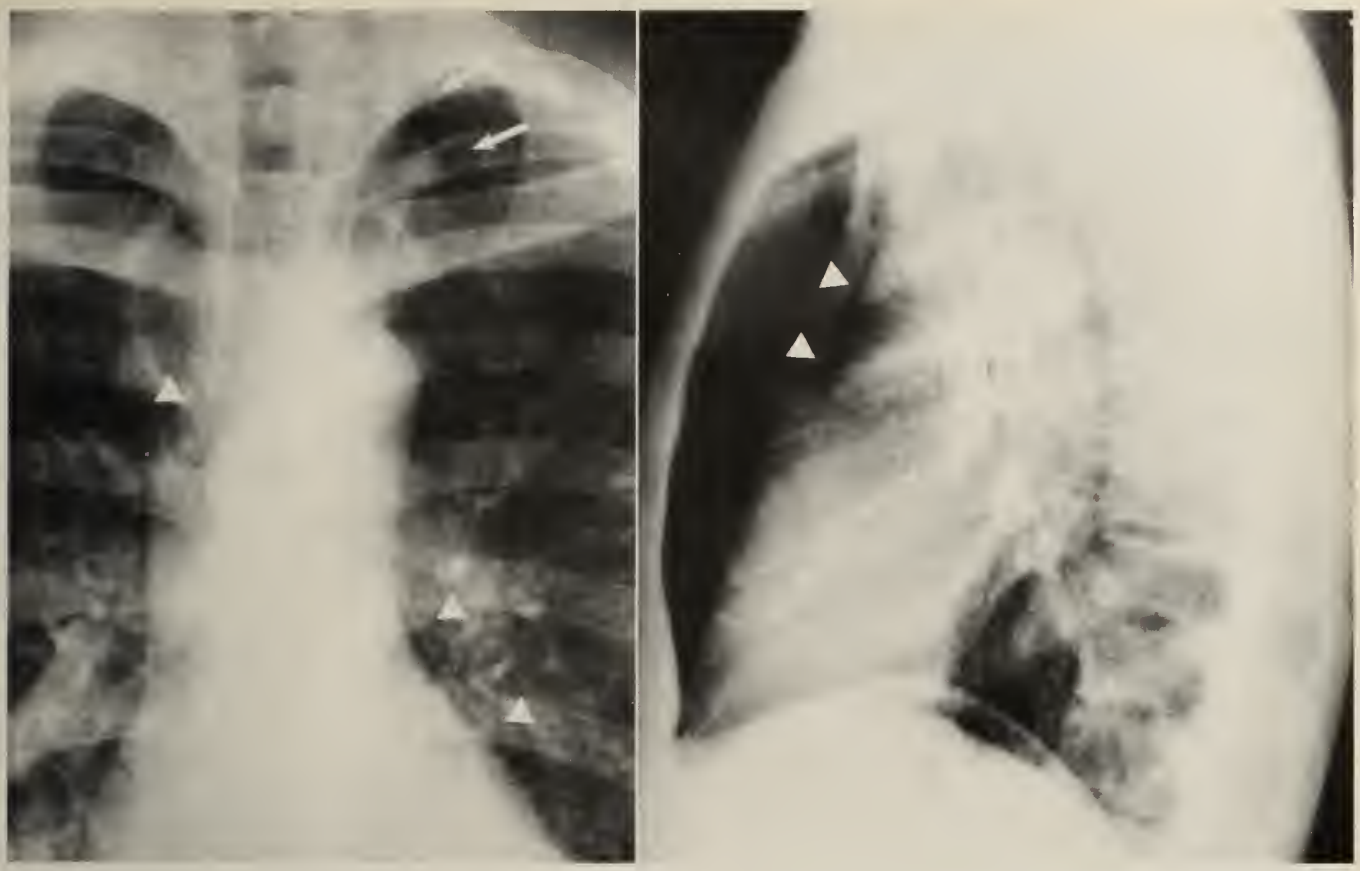

Figure 4.—Left, anteroposterior and, **Right,** lateral chest radiographs show subtle pneumomediastinum **(arrowheads)** and subcutaneous emphysema in the neck **(arrows).**

the night before his admission when he reports that he drank six beers and smoked alkaloidal cocaine. His chest radiograph showed pneumomediastinum and subcutaneous emphysema in the neck (Figure 4). The rest of his medical workup elicited no abnormalities. After eight hours of observation in the emergency department, the patient's chest pain resolved and his pneumomediastinum had decreased in size. He was discharged to be followed up by his physician in Mexico.

Discussion

Pneumomediastinum is classified as nontraumatic (primary or spontaneous) and traumatic (secondary). Spontaneous pneumomediastinum can be seen in adolescents following acute intermittent respiratory obstruction and may be associated with asthma, pertussis, pneumonia, emesis, retching, defecation, straining, weight lifting, or coughing. One report noted that half of all cases of nontraumatic pneumomediastinum were associated with parturition.[8] More recently we have become aware of an association between smoking (freebasing) alkaloidal cocaine ("crack") with the development of pneumomediastinum, probably related to a prolonged Valsalva's maneuver or to the use of positive pressure. Positive pressure is usually applied by a partner, either by direct mouth-to-mouth contact or through blowing into a cylinder.

Alkaloidal or free-based cocaine is created by combining cocaine with a basic solution such as ammonium and a solvent such as ether to create cocaine crystals, which are more volatile than cocaine salt.

The mechanism of primary pneumomediastinum is thought to be related to increased intra-alveolar pressure with the development of a pressure gradient between alveoli and surrounding blood vessels. The pressure gradient causes acute rupture of an overly distended alveolus, alveolar web, or bleb.[1,2] This may involve a negative-pressure gradient during a forced inspiration or a positive-pressure gradient during a prolonged breath-holding (Valsalva) maneuver. In addition, alkaline cocaine and other contaminants (benzoic acid, methanol, or sulfuric acid) on the alveolar wall may cause an inflammatory response and weakening of the adventitia, which may also lead to rupture. This latter mechanism may explain why the onset of symptoms is often delayed. After alveolar rupture, fine bubbles of air track along the vessels and bronchi, coalescing into larger air collections in the mediastinum. The free air may then decompress along the fascial planes of the trachea and esophagus and into the anterior mediastinum and subcutaneous soft tissues of the chest, neck, and axillary regions.

Clinical manifestations of pneumomediastinum include stabbing chest pain, pleuritic chest pain, dyspnea, the so-called mediastinal crunch (Hamman's sign), and subcutaneous emphysema. On a posteroanterior chest radiograph, lucency may be seen along the left heart border, indicating displacement of mediastinal pleura. Lucency indicative of subcutaneous emphysema within the soft tissues of the chest, the axillary region, and the neck may also be seen. On the lateral chest radiograph, air lucency may be seen outlining the hilar pulmonary vessels and extending along the fascial planes of the esophagus and trachea.

Although usually self-limited, this condition must be differentiated from esophageal perforation, a potentially life-threatening condition. A barium esophagogram may be necessary to evaluate these patients.

In the vast majority of patients, pneumomediastinum and symptoms will spontaneously resolve. Close outpatient medical care and follow-up chest films are appropriate for these patients.

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Topics in Primary Care Medicine

Evaluation of Hematuria in Adults

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

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Series' Editors

A small number of erythrocytes may be found in normal urine, but more than three to five erythrocytes per high-power field on a microscopic examination is generally considered abnormal. Hematuria is a common adult problem. In a recent population-based study, 13% of adults had asymptomatic hematuria. There is a general perception that hematuria is a serious problem and that potentially life-threatening causes must be vigorously ruled out. While an aggressive approach is clearly indicated in certain "high-risk" populations (such as the elderly), otherwise asymptomatic adults younger than 40 years rarely have serious occult diseases causing hematuria. In this article I will discuss the causes of hematuria and present an approach to evaluating hematuria for primary care providers.

Causes of Hematuria

Several studies have examined the causes of hematuria and have found that distinctions between gross and microscopic hematuria, or between hematuria present on one or several analyses, cannot be relied on to predict a benign process. Therefore, clinicians must consider the possibility that even a single episode of asymptomatic microscopic hematuria may indicate a serious disease. The frequency of specific causes of hematuria varies widely in currently reported studies, as Table 1 shows. These differences reflect the different methods, patient populations, and referral patterns. Many of these studies are from referred urologic populations and do not represent the patients seen in a primary care setting. Neoplasms, infections, and nephrolithiasis are common causes in these studies. Urethrotrigonitis is a poorly defined group of inflammatory disorders of unclear significance described in the older urologic literature. Many cases of hematuria have no clear cause despite an extensive workup. In the past these have been labeled "benign primary hematuria" or "essential hematuria." Many of these patients have glomerular abnormalities, such as immunoglobulin (Ig) A nephropathy.

In a recent study of patients with asymptomatic microscopic hematuria in a primary care setting, Mohr and coworkers found a low frequency of life-threatening urologic disease. The results of this population-based study should accurately reflect the causes of hematuria found in most primary care settings. Serious urologic disease, which included neoplasms, ureteral calculi, and hydronephrosis, was found in 2.3% of cases, and only 0.5% had bladder or renal carcinoma. Age was a significant risk factor for malignant diseases, and younger patients, particularly those younger than 55, did well over a seven-year observation period. Serious urologic disease was also more common in men than in women. Unfortunately, at this time there are no prospective population-based studies on hematuria to confirm these findings or identify other risk factors for serious disease.

The numerous causes of hematuria can be classified several different ways, and one example is shown in Table 2. The five major etiologic categories are glomerular, renal (nonglomerular), postrenal, hematologic, and false hematuria.

Glomerular

The most common cause of glomerular bleeding is glomerulonephritis. Acute glomerulonephritis, either primary or secondary to a systemic disease, is usually characterized by the sudden appearance of hematuria, proteinuria, and erythrocyte casts. The associated symptoms and selected serologic findings often help differentiate among the various causes of secondary glomerulonephritis, but a renal biopsy may be required to differentiate among the primary types of the disorder.

Primary glomerulonephritis may also present with only isolated hematuria without proteinuria or casts. Many patients with this disorder have been diagnosed as having "benign primary hematuria" in the past when extensive evaluations were unrevealing and the long-term prognosis appeared to be good. If a renal biopsy is done on these patients, as many as 15% reportedly show no abnormalities. A wide variety of lesions are found in the other 85% of cases, and a substantial proportion of these patients are found to have mesangial abnormalities and IgA deposits with immunofluorescent staining. The clinical manifestations of so-called IgA nephropathy range from asymptomatic hematuria following viral infections (Berger's disease) to systemic involvement as seen in Schönlein-Henoch purpura. Treatment is primarily supportive and the long-term prognosis generally good, but

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some patients do require therapy for progressive hypertension or renal insufficiency.

Another cause of hematuria that is thought to be glomerular in origin is strenuous exercise. Exercise-induced hematuria was documented in 18% of male runners in a marathon foot race. It is characterized by gross or, more commonly, microscopic hematuria during or shortly after strenuous exercise. Exercise-induced hematuria persists for 24 to 48 hours after the activity but is not associated with other signs or symptoms of renal disease. Although the bleeding is thought to be glomerular in origin, the long-term prognosis is excellent, and if the findings resolve within 48 hours, most experts agree that no further evaluation is indicated.

TABLE 1.—*Frequency of Common Causes of Hematuria*

Cause of Hematuria	*Frequency, %*
Neoplasm	2-18
Infection	0-24
Nephrolithiasis	4-25
Obstruction	0-3
Trauma	0-3
Glomerulonephritis	0-10
Prostatic hypertrophy	0-23
Urethrotrigonitis	1-24
No diagnosis	10-93

TABLE 2.—*Common Causes of Hematuria**

- Glomerular
  - IgA nephropathy
  - Other glomerulonephritis
  - Alport's syndrome
  - Benign familial hematuria
  - Strenuous exercise
- Renal (nonglomerular)
  - Renal infarct
  - Renal vein thrombosis
  - Tuberculosis
  - Pyelonephritis
  - Polycystic disease
  - Medullary sponge kidney
  - Interstitial nephritis—drug-related, infection, and the like
  - Neoplasm
  - Vascular malformations
  - Trauma
  - Papillary necrosis
- Postrenal
  - Nephrolithiasis
  - Tumors of lower urinary tract
  - Cystitis—infection, drug-related, radiation, idiopathic
  - Prostatitis
  - Foreign bodies of bladder or urethra
  - Urethritis
  - Benign prostatic hypertrophy
  - Obstruction
- Hematologic
  - Coagulopathy
  - Anticoagulation
  - Sickle cell anemia and trait
- False
  - Vaginal bleeding
  - Fictitious
  - Pigmenturia—porphyria, hemoglobinuria, myoglobinuria, food, drugs

*Modified from Abuelo (*Urology* 1983; 21:215-225).

Renal (Nonglomerular)

Nonglomerular renal lesions that may cause hematuria include a variety of disorders such as pyelonephritis, renal infarct, renal vein thrombosis, interstitial nephritis, papillary necrosis, and tumors. Of all renal tumors 90% are renal cell carcinoma, the second most common malignant neoplasm of the urinary tract. Renal cell carcinoma occurs predominantly in older patients; only 4% of cases are found before age 40. Approximately 60% of these cases present with hematuria, but various systemic presentations including hypertension, polycythemia, and fever are common. If these slow-growing tumors are detected early and surgically removed before the tumor reaches the capsule, the five-year survival may be as high as 67%.

Postrenal

Hematuria commonly results from postrenal causes such as nephrolithiasis, cystitis, prostatitis, and lower tract neoplasms, particularly transitional cell carcinoma of the bladder (the most common malignant disorder of the urinary tract). Unfortunately, as many as 22% of cases of transitional cell carcinoma are not associated with detectable hematuria. Again, if detected and treated early, lower urinary tract cancers generally have an excellent prognosis. Although benign prostatic hypertrophy may cause hematuria, other causes must be ruled out because the majority of patients will ultimately have another cause for the hematuria.

Hematologic

Hematologic causes of hematuria include coagulopathies, excessive anticoagulation, and hemoglobinopathies. Therapeutic anticoagulation or antiplatelet therapy generally does not cause hematuria, and underlying disease must be excluded. The sickle cell trait can cause microscopic or gross hematuria. The hematuria is usually painless and resolves spontaneously, but the mechanism is unknown. The sickle cell trait should also be considered in nonblacks as well, as the trait is widely distributed among the populations of southern Europe, the Middle East, North Africa, and India.

False Hematuria

False hematuria includes bleeding from other sources, such as the vagina or external genitalia, and pigmenturia. Pigmenturia is common with certain foods, such as beets, and drugs including phenazopyridine, methyldopa, and rifampin. Myoglobinuria and hemoglobinuria both cause positive urine dipstick tests in the absence of erythrocytes on microscopic examination. Fictitious hematuria can be exceedingly difficult to diagnose and is best ruled out by careful catheterization.

Evaluation

A cost-effective and rational approach to hematuria should always begin with a detailed history. In addition to questions related to the specific causes noted previously, such as recent strenuous exercise or a family history of renal disease, several other historical points are worth pursuing. Gross hematuria at the beginning or end of micturition sug-

gests a urethral or prostatic source. Clots may imply a postglomerular source. If the hematuria was preceded by an upper respiratory tract infection, the interval between symptoms is helpful—in Berger's disease, the hematuria begins with or shortly after an upper respiratory tract infection, but in glomerulonephritis that follows a streptococcal infection, there is a latent period of seven to ten days.

The physical examination should be directed to detect signs of acute glomerulonephritis such as hypertension and volume overload. The abdomen, pelvis, and prostate should be examined for masses or tenderness, and the urethral orifice must be visualized.

The laboratory evaluation of hematuria should be directed toward identifying potentially serious or reversible causes. Unless the findings of the history and physical examination point elsewhere, the initial laboratory evaluation of hematuria should be limited to a urine culture (to rule out subacute or asymptomatic bacterial infections), blood urea nitrogen, serum creatinine levels, and a urinalysis. If renal insufficiency is present, a separate evaluation of that abnormality should be undertaken, including the exclusion of dehydration, infection, and obstruction.

The urinalysis should not be delegated to a laboratory technologist. Urine dipstick tests may occasionally be falsely normal with low but significant levels of hematuria, particularly in the presence of ascorbic acid. The microscopic examination must be done on freshly spun urine to detect formed elements. Pyuria suggests an infectious or inflammatory process. Erythrocyte casts are highly suggestive of glomerulonephritis, and their presence can direct further evaluation. If no erythrocytes are seen, pigmenturia, such as hemoglobinuria or myoglobinuria, may be present.

A urine protein reaction of greater than 1+ on the dipstick in a patient with hematuria may point to a glomerular lesion, and a 24-hour urine collection should be done to quantify the urinary protein. Infrequently, proteinuria may also result from gross hematuria with hemolysis. Although the diagnostic yield is low, an intravenous pyelogram is indicated in patients with substantial proteinuria to rule out the renal causes of hematuria and proteinuria, such as reflux nephropathy, renal tuberculosis, papillary necrosis, and renal cell carcinoma. If the pyelogram is unrevealing, the patient most likely has glomerulonephritis, and an appropriate evaluation should be initiated. If the proteinuria remains unexplained and the protein concentration is greater than 0.15 grams per day (150 mg per day), the patient should be referred to a nephrologist for further evaluation and a possible renal biopsy.

Isolated hematuria, present in a substantial number of patients, is defined as hematuria without other symptoms or evidence of infection, renal insufficiency, or proteinuria. Patients with isolated hematuria have generally undergone a number of additional studies, such as intravenous pyelography and cystoscopy, to rule out serious disorders. This approach is well accepted in adults older than 50 years where the incidence of malignancy is high, but some investigators feel the risk of iatrogenic complications and added cost may outweigh the benefit in young adults. Based on the data of Mohr and others, many young persons with isolated hematuria will be investigated needlessly to find those few with a dangerous and reversible process. The consequences, however, of an undiagnosed malignant lesion in a young adult are serious, even if rare. There is yet no consensus on whether to evaluate isolated hematuria in young adults, and most practitioners are awaiting further studies and the elucidation of risk factors before changing their approach to this problem.

If a clinician decides to further evaluate a patient with isolated hematuria, or if a patient's symptoms warrant additional testing, an intravenous pyelogram, cystoscopy, and urine cytologic examination should be done. A well-done pyelogram is sensitive, at least 95%, in detecting renal anatomic abnormalities that can be further evaluated with sonography, computed tomography, or needle aspiration if necessary. Cystoscopy is considered the best diagnostic test to rule out lower genitourinary tract disease, and it may localize the source of bleeding from one or both ureters. A cytologic examination of voided urine will often detect high-grade bladder tumors. As many as 95% of grade III and invasive bladder tumors are detected by a cytologic examination of three consecutive urine specimens. A cytologic examination is less likely to detect low-grade tumors of the bladder and cannot be used alone to exclude serious disease.

If the above studies are unrewarding, consideration should be given to checking coagulation studies and doing hemoglobin electrophoresis to rule out the sickle trait. First-degree relatives should also have their urine examined to identify hereditary hematuria.

Patients without a specific diagnosis after an appropriate evaluation can be managed in one of several ways. If the bleeding is localized to one kidney and is serious or results in progressive anemia, angiography may be indicated to identify vascular malformations. Episodes of hematuria following upper respiratory tract infections probably represent IgA nephropathy, and the patient should be observed for the development of hypertension or azotemia. If a patient is older than 40 years and has hematuria of an unclear cause, most urologists suggest close follow-up for at least three years with a repeat urinalysis and cytologic examination every six months and yearly cystoscopy and intravenous pyelography.

Additional studies are helpful in certain circumstances. Phase contrast microscopy, if properly done, is able to distinguish erythrocytes of glomerular origin (which display a typical dysmorphism) from those of postrenal sites. Some trained observers can detect this dysmorphism using light microscopy as well. Several studies support the efficacy of phase contrast microscopy, but it has yet to gain widespread use. If IgA nephropathy is present, a biopsy of normal skin reveals IgA deposits in 20% to 50%, and serum IgA levels are elevated in about 50%. Skin biopsy and serum IgA levels are insensitive tests for diagnosing IgA nephropathy and are of use only in confirming suspected cases.

A renal biopsy is of little use in the evaluation of isolated hematuria. In these cases, most glomerular lesions identified do not respond to any current therapy. In addition, the renal biopsy provides little prognostic information in isolated hematuria, as most patients follow a benign course regardless of the histopathology identified.

In summary, hematuria clearly has a multitude of causes, many of which are benign. Referral to a urologist is appropriate if the findings of an intravenous pyelogram or cytologic examination suggest malignancy or if cystoscopy is indicated to rule out lower tract disease. A nephrologist should be consulted if renal insufficiency, acute glomerulo-

nephritis, or significant proteinuria is present. Using a well-reasoned and logical approach, primary care providers are frequently able to define the cause without unnecessary expense or risk to the patient.

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Book Review

The Western Journal of Medicine does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.

Heart Disease in Infants, Children, and Adolescents

Fourth Edition—Edited by Forrest H. Adams, MD, Emeritus Professor of Pediatrics and formerly Head, Division of Cardiology, Department of Pediatrics, University of California, Los Angeles, School of Medicine; George C. Emmanouilides, MD, Professor of Pediatrics, University of California, Los Angeles, School of Medicine, and Chief, Division of Pediatric Cardiology, Harbor-UCLA Medical Center, Torrance, California; and Thomas A. Riemenschneider, MD, Associate Dean; Professor of Pediatrics, Epidemiology, and Biostatistics; and formerly Chief, Division of Pediatric Cardiology, Case Western Reserve University School of Medicine, Cleveland. Williams & Wilkins, 482 E Preston St, Baltimore, MD 21202, 1989. 1,048 pages, price not known.

The latestest edition of *Heart Disease in Infants, Children, and Adolescents* is a substantially enlarged version of a classic textbook on cardiovascular disease in the young patient. The new edition contains 56 chapters by 108 experts encompassing a wide spectrum of topics. The book combines time-proven facts and principles with newer concepts and technology developed in the six years since the third edition was published.

In the General Cardiology section, the noninvasive diagnosis chapter includes two parts on ultrasound, echocardiography and Doppler echocardiography, and a part on magnetic resonance imaging and positron emission tomography, reflecting the increasing prominence of noninvasive imaging in pediatric cardiology. The invasive methods chapter updates standard cardiac catheterization techniques, including a section on indications for surgical procedures without catheterization. The transvascular catheter approach to tissue diagnosis and therapy is discussed by experts on myocardial biopsy and balloon dilatation procedures for stenotic valves and vessels. Techniques for catheter closure of patent ductus arteriosus and intracardiac defects are also evaluated. Other parts discuss electrocardiography, exercise testing, nuclear cardiology, angiocardiography, and electrophysiology.

The Congenital Defects section presents the broad spectrum of congenital disease, with updates on medical and surgical techniques. The Fontan and Norwood operations are of particular interest. An example of the increasing scope of the book is the chapter on the adult with congenital heart disease. Patients with congenital heart disease are surviving into adulthood in increasing numbers, with more complex lesions presenting new challenges to both pediatric and adult cardiologists. The problems of the pregnant young woman with congenital heart disease are given special attention.

Perhaps the most interesting because of its diversity is the Special Problems section, which addresses 18 different topics. In addition to the problems of adults and pregnancy mentioned above, prenatal diagnosis of congenital anatomic disease and dysrhythmias; hypertension, both pulmonary and systemic; cardiomyopathy, shock, surgical techniques, and transplantation are discussed. There are new chapters on psychosocial and ethical considerations—important problems in pediatric cardiology because of the high risk to many patients and high financial cost for diagnosis and treatment.

Other sections address infectious disease, metabolic and nutritional problems, and cardiac disease as part of a systemic illness. The continuing problem of infectious endocarditis, the resurgence of rheumatic disease, and new knowledge of metabolic diseases emphasize the value of these sections.

This large text is a valuable reference for the physician with a special interest in cardiovascular disease in the young. It is neither a condensed version of pediatric cardiovascular disease suitable for rapid review nor does it replace the several excellent journals reporting newer investigations. The book does present a huge fund of information, with an excellent bibliography evaluated by clinicians and scientists who are experts in the areas they represent. In this category the fourth edition is one of the best textbooks available.

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Medical Practice

Malpractice Litigation as a Factor in Choosing a Medical Specialty

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Although many factors have been identified as influencing specialty choice, there has been no research focusing on the effects of the current climate of medical practice, including litigation. Our study examines medical students' and residents' awareness of the malpractice litigation environment and their reasons for choosing a specialty that is at either high or low risk for malpractice suits. Longitudinal data showed that students continued to choose high-risk specialties (40%) even though they perceived problems in the current climate of litigation. Among the reasons for their choices were enjoyment and being able to practice in a procedure-oriented specialty that is effective in its mode of treatment. Those who chose low-risk specialties (60%) rated as important the variety of diseases seen and the opportunity to know patients well. Issues related to the malpractice climate were important only to those who switched from a high- to a low-risk specialty. These findings have implications for professional staffing needs.

(Pyskoty CE, Byrne TE, Charles SC, et al: Malpractice litigation as a factor in choosing a medical specialty. West J Med 1990 Mar; 152:309-312)

Many factors have been identified as influencing medical students' specialty choices. These include race,[1] sex,[2-8] intellectual ability,[9] aptitude for science,[10] academic performance,[11,12] clinical clerkship experience,[13] attitudes,[14] personality characteristics,[9,15-17] and life-style preferences.[18] We could not find any research that establishes whether recent changes in medical practice, including the current climate of malpractice litigation, influence a student's decision about a specialty.

Key issues in specialty choice include the shift that occurs during medical school and factors influencing it. The stability rate of specialty selection in previous research ranges from 25% to 57%.[19-21] A study by Katz and co-workers found that of the 50% of students who changed their specialty preference during medical school, 84% did so because of negative factors related to the initial choice while only 16% did so because of positive factors found in a new choice.[22]

Our study was designed to examine students' and residents' attitudes toward changes in medical practice, focusing especially on the malpractice litigation atmosphere, and the influence of these changes on specialty choice. The design included the use of longitudinal data, by which we could observe changes in specialty preference relative to shifts in attitudes.

We classified specialties into those at high risk or low risk for malpractice suits. We then identified the factors involved in the decision to practice in a high-risk specialty rather than one in which the probability for suit, and consequently the cost of malpractice insurance premiums, is lower. It is our hypothesis that perceived problems in the current climate of medical practice, especially those involving malpractice issues, cause students to switch from high- to low-risk specialties.

Methods

This is the follow-up of a study conducted in the fall of 1985. In that study (time 1) a questionnaire regarding awareness of the current malpractice litigation climate and specialty choice was mailed to a random sample of 260 students, stratified by sex with equal numbers of men and women, representing all four years at a medical college in a major city. A 72% response rate (n = 187) was obtained.

Time 1 respondents reported that they would most likely go into internal medicine (26.8%), family practice (13.4%), and pediatrics (13.4%). The specialties perceived as being at high risk for malpractice suit, and the percentage of respondents preferring them, were surgery and its subspecialties (17%), obstetrics and gynecology (5%), and anesthesiology (2%).

The time 2 study, carried out three years later, consisted of a questionnaire sent to the time 1 respondents. The sample size was decreased to 155 from 187 because of dropouts, transfers, and an inability to locate respondents.

Questions probed awareness of the malpractice litigation climate and attitudes toward other changes in the practice of medicine. In addition, 26 items elicited the relative importance of various factors in selecting a medical specialty. This list was derived in part from Tardiff and associates[18] and was presented on a five-point scale (1 = not important, 5 = very important). The recent role of the acquired immunodeficiency syndrome as a factor in career or specialty choice or both, as suggested by Cotton, was not included.[23]

The designation of high- or low-risk specialty in this study was based on the rate classification used by the Illinois State Medical Inter-Insurance Exchange, a physician-owned insurer.[24] This classification sets insurance rates in terms of seven risk categories, and we designated as high risk those

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specialties in and above category 4. These specialties are anesthesiology, emergency medicine, obstetrics and gynecology, and surgery and its subspecialties. The low-risk groups included all other specialties.

The data were coded and analyzed using the Statistical Package for the Social Sciences x.[25] Answer categories—that is, agree and strongly agree, important and very important—were collapsed to facilitate analyses. Where appropriate, *t* tests, χ^2, and one-way analyses of variance were done.

TABLE 1.—*Characteristics of the Time 2 Sample**

Characteristics	*Sample, (n=102), %*
Race	
White	68.6
Black	14.7
Hispanic	10.8
Asian	4.9
Marital status†	
Single	52.9
Married	43.1
Divorced	2.0
Most popular specialties	
Internal medicine	23.5
Obstetrics-gynecology	16.7
Family practice	14.7
Psychiatry	5.9
Radiology	5.9

*Mean age, 27 years; male to female ratio, 53:49.
†The percentages for "Marital status" total 98% because 2% of physicians did not respond to this section of the questionnaire.

Results

The final response rate was 66% (n = 102). The demographic characteristics of the time 2 sample are described in Table 1. There were no differences between time 2 respondents and nonrespondents on any of the time 1 variables. The most popular specialty choices among time 2 respondents were internal medicine (23.5%), obstetrics and gynecology (16.7%), and family practice (14.7%). A low-risk specialty was chosen by 60% (n = 61), while 40% (n = 41) chose one at high risk for suit. These two groups did not differ significantly in age, sex, race, or marital status.

Reasons for Specialty Choice

The primary reasons for choosing a specialty are listed in Table 2. Malpractice concerns—rate of suits and costs of insurance premiums—were among the least important factors.

Those who chose high-risk and low-risk specialties differed significantly in their reasons for specialty choice. The high-risk group was more likely to rate as important the opportunity to do operations and other procedures, effectiveness of treatments in the specialty, their own technical competence, and scientific knowledge associated with the specialty.

The low-risk group, on the other hand, was considerably more likely to be influenced by the opportunity to see a wide variety of diseases, to know patients well, and to handle many difficult diagnostic problems in the specialty.

Stability of Specialty Choice—Comparison of Changes Within and Across Risk Groups

Of the 100 students who had indicated a specialty at both time points, 53% (n = 53) changed specialties during their

TABLE 2.—*Factors in Choosing a High- or Low-Risk Specialty*

	Percent Indicating Factor Is Important			
Factor	*Overall (n=102), %*	*High Risk (n=40), %*	*Low Risk (n=62), %*	P*
Aptitude for material in specialty	70.6	67.5	72.6	
Opportunity to see a wide variety of diseases	68.6	47.5	82.3	<.001
Organ system or type of disease seen	66.3	72.5	62.3	
Opportunity to know patients well	65.3	47.5	77.0	<.01
Patients appreciate physician's efforts	64.4	75.0	57.4	
Ability or technical competence	59.4	87.2	41.9	<.001
Effectiveness of treatments	59.0	87.2	41.0	<.001
Opportunity to perform operations or procedures	55.9	95.0	30.6	<.001
Scientific knowledge or precision	54.9	70.0	45.2	<.05
Presence of many difficult diagnostic problems	51.0	30.0	64.5	<.01
Opportunity to add new knowledge to specialty	49.0	57.5	43.5	<.05
Faculty or house staff as role models	48.5	38.5	54.8	
Site of residency training	42.6	41.0	43.5	
Opportunity to live in urban, rural, or suburban area	42.6	41.0	43.5	
Greater flexibility in time management	41.2	30.0	48.4	<.01
Prediction of manpower needs	31.4	22.5	37.1	<.01
Quality of medical school teaching	26.5	30.0	24.2	
Length of postgraduate training	26.5	12.5	35.5	<.01
High prestige within the profession	24.8	25.0	24.6	
Financial rewards of practice	23.5	35.0	16.1	<.05
Experience of self or family member as patient	19.0	15.0	21.7	
Low rate of malpractice lawsuits	14.7	7.5	19.4	<.001
Low malpractice insurance premiums	12.9	7.7	16.1	<.001
Influence of family or close friends	10.9	7.5	13.1	<.05
Interactions with students in medical school	9.1	....	14.8	<.001
Debts from college or medical school, or both	3.9	....	6.5	

*χ^2 values based on comparisons between high-risk and low-risk groups.

TABLE 3.—*Reactions to Changes in the Climate of Medical Practice*

Reaction or Change	Total Agreeing or Strongly Agreeing, %	Specialty Choice: High Risk, %	Specialty Choice: Low Risk, %	P*
Defensive medicine raises the cost of medical care	76.2	70.0	80.3	
Doctors are ordering tests and procedures even when they are not medically indicated as a defense against malpractice suits	73.3	75.0	72.1	
It is becoming more difficult for doctors to uphold the ideals of medicine	70.3	77.5	65.6	
Malpractice litigation is having a negative effect on quality of care	68.3	77.5	62.3	
The current malpractice climate has caused a deterioration in the quality of the doctor-patient relationship	68.3	77.5	62.3	
Doctors are stopping certain high-risk procedures that are medically indicated because of fear of being sued	48.5	62.5	39.3	<.05
The probability of being sued sometimes enters into my thoughts of specialty choice	43.0	61.5	31.1	<.01
Defensive medicine raises the quality of care	17.8	22.5	14.8	
Doctors are spending more time than they used to with their patients	16.8	15.0	18.0	
I am planning to practice in an area where rates and fees are lower	15.3	21.6	11.5	
Doctors are decreasing their patient loads	11.9	10.0	13.1	
The number of malpractice suits is an accurate reflection of the incidence of actual malpractice	7.9	7.5	8.2	

*χ^2 values based on comparisons between high-risk and low-risk groups.

medical school years. Of those who had originally chosen a low-risk specialty (n = 73), 32% (n = 23) preferred a different one within the low-risk category at time 2, and 23% (n = 17) switched to a high-risk specialty. Those who started out in the low-risk group and remained in it (56% of the total sample) were significantly more likely than those who switched to a high-risk specialty to do so because of the wide variety of diseases seen, many difficult diagnostic problems, and flexible working hours. They were also significantly more likely to report that low rates of malpractice suits and insurance premiums were factors in their choice. Those who switched from low- to high-risk specialties (17% of the total sample) were significantly more likely to rate having done so because of their own ability or competence, the opportunity to do specific procedures and to add new knowledge to the specialty, the effectiveness of treatments, and the feeling that patients appreciate the physician's efforts.

Of those starting out in the high-risk group (n = 27), 30% (n = 8) switched within risk group and 18.5% (n = 5) changed to a low-risk specialty. For those who started out and continued in high-risk specialties (22% of the total sample), the opportunity to do specific procedures was a significant factor in their decision.

Those who switched from high- to low-risk specialties (5% of the total sample) reported as important the lower rates of suits and premiums, the length of postgraduate training, the opportunity to know patients well, and interactions with students in medical school.

Reactions to Changes in the Climate of Medical Practice

Table 3 presents respondents' views of the changing medical environment. When asked to rate, on a five-point scale (5 = positive), the influence of three major forces on quality of care, prepaid group practices received a mean rate of 2.4, diagnosis-related groups a mean rate of 2.1, and the current malpractice climate was rated a mean of 1.97. Further analyses showed that 68.3% agree that the increasing rate of malpractice litigation has an adverse effect on quality of care and contributes to a deterioration in the quality of physician-patient relations. Furthermore, 58.4% of the respondents disagree that physicians should take any patient who presents for treatment, and greater than 70% think it is becoming more difficult for physicians to uphold the ideals of medicine.

High-Risk and Low-Risk Differences

When these attitudes and perceptions were analyzed separately, high- and low-risk groups differed significantly on only 2 of the 23 items, 12 of which are listed in Table 3. The high-risk group was significantly more likely to agree that they had thought about the probability of a malpractice suit when choosing a specialty and that physicians are stopping certain medically indicated, high-risk procedures because of the fear of being sued.

Changes Over Time

Respondents were significantly more likely at time 2 than at time 1 to agree that it is becoming more difficult to uphold the ideals of medicine ($t = 5.41$, $P < .001$) and that the current malpractice litigation climate has caused a deterioration in the quality of the physician-patient relationship ($t = 2.06$, $P < .05$). These findings remained when attitudes were analyzed separately for high-risk and low-risk specialty respondents. In addition, those who chose a low-risk specialty were more likely at time 1 than at time 2 to have considered both the probability of being sued and the cost of malpractice insurance in choosing their specialty.

Discussion

This study begins to examine whether medical students' and residents' perceptions of the changing medical environment influence specialty choice. Study results failed to support our hypothesis that an increased awareness of the malpractice climate would motivate students to avoid high-risk specialties. Consistent with previous research, 52% of respondents changed their specialty choice between times 1 and 2, a period when they were exposed to the actual climate of practice, including the litigation environment. Whereas only 5% switched out of the high-risk category, 17% changed in the opposite direction.

Although respondents perceived problems in the current climate of medical practice and litigation, this did not discourage them from entering high-risk specialties. In fact, the number of those choosing high-risk specialties increased from 27% (n = 27) at time 1 to 40% (n = 41) at time 2. This represents a slightly higher figure than the 32% of all medical school graduates surveyed nationally in 1987 who had

chosen a high-risk specialty.[26] The shift toward high-risk specialties, however, is similar to that found by Babbott and colleagues, who observed changes in students' preferences between the time they took the medical college admissions test and graduated from medical school.[21]

Of the total group at time 2, those who chose high-risk specialties reported doing so because they enjoy and feel adept at practicing a procedure-oriented specialty that is effective in its mode of treatment. This is in sharp contrast to the opinion held by McCarty that students choose high-technology specialties because of high pay and prestige and low emotional involvement.[27] The low-risk group, on the other hand, chose their specialty for the variety of diseases seen and the opportunity to know patients well. In neither group were malpractice litigation issues significant. We did find, though, that those who switched from a high- to a low-risk specialty rated the malpractice climate as important in their decision. This may be related to a recent finding of the American Association of Medical Colleges that 72% of senior medical students surveyed reported malpractice premium costs as a deterrent to choosing obstetrics and gynecology as their specialty.[28] Thus, the adverse influence of litigation, although not important to those who chose high-risk specialties, is significant for those who switch from a high- to a low-risk specialty.

Our respondents perceive the litigation environment as having a detrimental effect on cost and quality of care as well as the nature of the physician-patient relationship. Most disturbing is the finding that most respondents, many about to enter practice, think it is becoming more difficult to uphold the traditional ideals of medicine. Practitioners, too, are struggling with the disparities between the ideal and the real, as reflected on by Relman and others.[29-31] During the three-year period between studies, these concerns increased substantially. This may be explained in part by the fact that students are forced to practice defensively, which contradicts the ideals taught in medical school and residency.

Respondents who choose high-risk specialties appear acutely aware of the influence of the litigation environment on their specialty, yet may be unaware of or deny the effects that a lawsuit might have on them personally. Charles and co-workers found that 22% of physicians interviewed reported that their malpractice litigation experience was the most stressful event of their entire life.[32] If students were more cognizant of the personal and professional repercussions of being sued, they might not enter a field that is associated with a higher rate of litigation. On the other hand, although students may be fully aware of the serious effects a lawsuit may have on their lives, they may use the psychological defense mechanism of denial, which shields them from consciously considering this important issue. Another explanation for choosing a high-risk specialty may be the simple fact that the positive aspects attracting students to these specialties far outweigh any negative factors.

Our study yielded a larger percentage of students entering high-risk specialties than occurs nationally. This may be due to the greater percentage of women who chose obstetrics and gynecology in our sample. The initial study design called for an equal distribution of men and women. Nationally, however, women make up only about a third of the resident work force. Furthermore, women constitute about 45% of the obstetrics and gynecology residents nationally compared with 65% in our study. Thus, our study is overrepresentative of women who have chosen this high-risk specialty.

That the current climate of medical malpractice litigation has influenced these medical students' and residents' attitudes toward their profession is clear. The effect on specialty choice, however, is important only in regards to those who changed from high- to low-risk specialties during the period of the study. The current trend is that students are moving away from low-risk specialties, especially those associated with primary care.[27,33] This study suggests that concerns about malpractice litigation, though not a powerful factor in specialty choice, may influence some students to counter the trend and choose a specialty at low risk for malpractice litigation.

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Information

A Simplified Screening Test for the Diagnosis of Allergy

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The Quidel allergy screen is a relatively rapid (less than 2 hours) multiallergen dipstick method for detecting specific immunoglobin E antibodies in serum. It was developed to answer the need of primary physician nonspecialists in allergy for a convenient in-office screening test for diagnosing allergy. The new test was evaluated against the benchmark diagnostic skin tests and the radioallergosorbent serologic tests for sensitivity, specificity, accuracy, and technical feasibility in an office setting. It was found that while the Quidel allergy screen lacks the specificity of the standard tests, its overall sensitivity, as defined by the percentage of patients with positive skin reactions who also tested positive with the Quidel screen (68%), its ease of use, and its rapidity warrant its consideration as a screening tool for confirming a possible case of allergy.

(Imam AA, Novey HS, Orgel HA, et al: A simplified screening test for the diagnosis of allergy. West J Med 1990 Mar; 152:313-316)

The cumulative prevalence of the classic allergic diseases—that is, allergic rhinitis, allergic asthma, atopic dermatitis, and allergic urticaria—probably exceeds 15% of the general population.[1] To confirm a diagnosis of allergy, however, the history must be supplemented by the finding of specific immunoglobulin (Ig) E antibodies to allergens encountered by the patient.

Laboratory measurements of total serum IgE and eosinophil levels correlate insufficiently with the diagnosis of allergy to be used alone as confirmatory tests.[2,3] While diagnostic skin tests remain the benchmark for identifying relevant IgE antibodies,[4] the applicability of skin tests for nonspecialist physicians who treat the bulk of the affected population is limited. More readily accessible serologic tests for specific IgE antibodies done in commercial laboratories are based on the radioallergosorbent test (RAST). These in vitro tests in turn have decreased sensitivity, cost-effectiveness, and timeliness compared with the skin test.[5]

An ideal screening test for allergy would detect IgE antibodies for six to nine representative allergens,[6,7] be as sensitive and specific as the skin test, as cost- and time-effective, and designed for use in a primary physician's office without complex equipment or highly specialized personnel.

A new method for measuring allergen-specific IgE antibodies in the serum uses a multiallergen dipstick in an enzyme-based immunoassay designed for visual detection by color intensity in less than two hours. We will refer to the assay as the Quidel allergy screening test.

The purpose of our study was to compare the results of the Quidel allergy screening test with those of the commercially available RAST (Phadebas) and of skin tests (prick and intradermal) for detecting specific IgE antibodies in atopic persons.

Patients and Methods

Subjects

A total of 132 patients judged to be atopic were studied at three independent medical centers. Atopy is defined as the ability to form IgE antibodies to allergens present in natural or physiologic amounts in a person's environment. Patients with symptoms suggestive of an allergic cause were skin-tested. Allergy is a disease or reaction associated with an IgE-mediated mechanism. Patients with positive skin tests were asked for a specimen of their serum, and RAST and Quidel allergy screening tests were carried out. An informed consent was obtained for each patient, and the study was approved by the appropriate human subjects review committee at each location.

Skin Tests

Initially, skin tests by the prick method were done on patients' backs. If the results of these tests were negative or equivocal, intradermal tests were then done on the arms. All centers used the same lots of 1:20 weight-per-volume concentrations in a 50% glycerol and saline solution for prick testing and 1:1000 weight-per-volume concentrations for intradermal tests made by Hollister-Stier, Inc, Spokane, Washington. None of the patients had received antihistamines for 48 hours before the skin testing, and none were taking the longer-acting antihistamines. Nine allergens were applied, and saline and histamine controls were used. The skin test

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ABBREVIATIONS USED IN TEXT

Ig = immunoglobulin
RAST = radioallergosorbent test

data were recorded as wheal and flare and measured in millimeters of greatest diameter to avoid any variation in their interpretation among the different centers. The prick and intradermal skin tests were graded from 0 to 4+ according to the following criteria:

Grade	*Wheal, mm*	*Flare, mm*
Negative	Equal to saline	Equal to saline to 4
1+	Greater than saline to 4	5 to 9
2+	5 to 9	10 to 14
3+	10 to 14	15 to 19
4+	15 and up	20 and up

Skin tests were considered positive if the reaction to the prick or intradermal test was 2+ or higher.

Quidel Allergy Screen Test

Serum specimens were collected from patients and stored at −20°C until the Quidel tests were done in batches. An aliquot of the same serum was stored frozen for the Phadebas RAST assay, and another aliquot was kept for evaluation in the manufacturer's laboratory.

The Quidel allergy screening assay was carried out as a field procedure by the participating investigators according to the manufacturer's instructions. The assay uses a polyclonal antibody linked with an enzyme, alkaline phosphatase, for facilitating visual interpretation of the results. Nine common allergens were tested, as follows: house dust, mite *(Dermatophagoides farinae)*, timothy grass, short ragweed, birch, *Alternaria* species, milk, and cat and dog dander, all obtained from Hollister-Stier, Inc. The allergens were immobilized on a ten-pad dipstick with a negative control in the center. Briefly, the test is done by immersing the allergen dipstick in the patient's serum for 30 minutes. This step enables any specific IgE to bind to the allergen on the dipstick. After thorough rinsing with tap water to remove unbound components, the dipstick is immersed for 30 minutes in a solution containing polyclonal anti-IgE conjugated with alkaline phosphatase. After another rinsing with tap water, the dipstick is immersed in the substrate solution for another 30 minutes. The dipstick is blotted, dried, and read visually. A blue color for a given allergen pad in comparison to the negative control pad indicates the presence of allergen-specific IgE.

Radioallergosorbent Test

The RAST test was done by an outside reference laboratory (Specialty Medical Laboratory, Los Angeles) using the modified Phadebas RAST procedure according to the manufacturer's package insert (Pharmacia, Piscataway, New Jersey).

Data Analysis

The diagnostic sensitivity, specificity, and predictive value of positive and negative test results were calculated for each allergen by standard 2 × 2 contingency methods. Sensitivity refers to the percentage of patients with positive skin test responses who have a positive response on the Quidel allergy screening test; specificity refers to the percentage of patients with no skin test responses who have a negative response on the Quidel test. Accuracy refers to the percentage of positive and negative Quidel test results compared with the true-positive and -negative skin test status.

In addition, both serologic tests were evaluated in the role of a screening test by comparing the number of patients who had a positive Quidel or RAST (to any allergen) with the actual number of atopic patients in the study. Ideally, those patients testing positive would be referred to an allergist for more comprehensive evaluation and testing.

Results

The ages of the 132 patients studied ranged from 7 to 65 years, with a mean of 23.8 years. Using skin tests as the standard, the results of the Quidel and RAST tests were compared with combined prick and intradermal skin tests. Table 1 shows the correlation of positive skin tests with positive Quidel and RAST test results for each allergen tested. The sensitivity for the nine allergens overall is 68.5% for the Quidel screen and 42.1% for RAST. For individual aller-

TABLE 1.—*Positive Skin Tests Correlating With the Quidel Allergy Screen (QAS) and the Radioallergosorbent Test (RAST) for Individual Allergens and Overall**

Allergen	*Pos Skin Tests, No.*	*Pos QAS, No.*	*Sensitivity, %*	*Pos Skin Tests, No.*	*Pos RAST, No.*	*Sensitivity, %*
House dust	107	78	72.9	108	52	48.1
Mite	88	69	78.4	88	45	51.1
Timothy grass . . .	95	71	74.7	96	79	82.3
Alternaria sp	76	43	56.6	77	27	35.1
Milk	14	10	71.4	36	1	2.8
Birch	78	36	46.2	78	30	38.5
Cat dander	61	53	86.9	96	36	37.5
Dog dander	92	67	72.8	94	7	7.4
Short ragweed . .	82	48	58.5	82	41	50.0
All 9 allergens . . .	693	475	68.5	755	318	42.1

Pos = positive

*See text for explanation of discrepancies in number of positive skin test results in two columns above.

TABLE 2.—*Negative Skin Tests Correlating With the Quidel Allergy Screen (QAS) and the Radioallergosorbent Test (RAST) for Individual Allergens and Overall**

Allergen	*Neg Skin Tests, No.*	*Neg QAS, No.*	*Specificity, %*	*Neg Skin Tests, No.*	*Neg RAST, No.*	*Specificity, %*
House dust	12	4	33.3	13	11	84.6
Mite	31	14	45.2	33	28	84.8
Timothy grass . . .	32	31	96.9	33	32	97.0
Alternaria sp	52	40	76.9	53	50	94.3
Milk	66	35	53.0	96	93	96.9
Birch	47	35	74.5	49	45	91.8
Cat dander	10	0	0.0	10	10	100.0
Dog dander	15	5	33.3	15	14	93.3
Short ragweed . .	44	34	77.3	47	43	91.5
All 9 allergens . . .	309	198	64.1	349	326	93.4

Neg = negative

*See text for explanation of discrepancies in number of negative skin test results in two columns above.

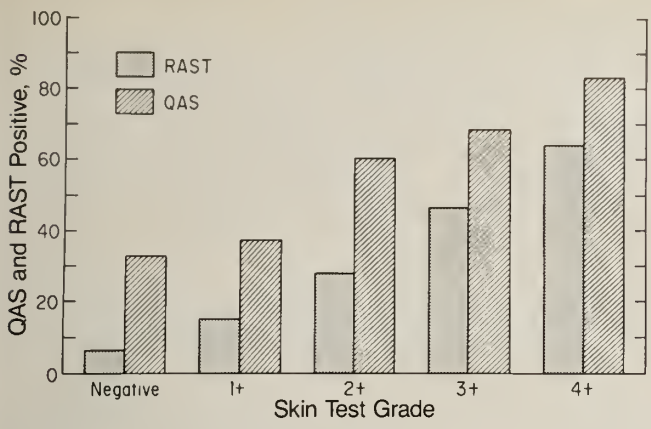

Figure 1.—Skin test reactivity grades to at least 1 of the 9 allergens applied are compared with the reaction rate of the serologic radioallergosorbent test (RAST) and the Quidel allergy screen (QAS). The percentage of reactivity increases as the skin test grade increases. For a 4+ skin test, 62% of the RAST and 82% of the QAS results were positive.

gens, the highest sensitivity was for cat dander (86.9%) with the Quidel assay and timothy grass (82.3%) with RAST. The lowest sensitivity for an allergen was birch (46.2%) with the Quidel screen and milk (2.8%) with RAST. It should be noted that there was a total of 62 more positive skin tests obtained with RAST than were obtained by the Quidel allergy screening procedure (755 versus 693, respectively, Table 1). Of these, 57 were accounted for by the manufacturer's change in the binding procedures for two allergens, milk (22 less by the Quidel test) and cat dander (35 less by the Quidel test) when these were found to be technically deficient. The remaining 5, for the total of 62 less, were due to the failure of the field investigators to record their results.

Table 2 shows the correlation of negative skin tests with negative Quidel and RAST results. As shown, the specificity for the nine allergens overall is 64.1% with the Quidel screen and 93.4% with RAST. When one looks at individual allergens, the highest specificity was for timothy grass (96.9%) with the Quidel screen and for cat dander (100%) with RAST. The lowest specificity was for cat dander (0%) with the Quidel screen and house dust (84.6%) with RAST. The positive predictive value for all nine allergens was 81.1% with the Quidel screening test and 93.3% with RAST. The negative predictive value was 47.6% with the Quidel test and 42.7% with RAST. The accuracy for all nine allergens was 67.2% with the Quidel screening test and 58.3% with RAST. Again, there is a discrepancy between those negative skin tests subjected to the Quidel screen of 40 less than to the RAST (309 versus 349, respectively, Table 2). The change in the milk allergen accounts for 30, and 10 are due to a failure to record field test results. Figure 1 compares the scoring of the skin test reactivity with the two serologic tests. The percentage of positive Quidel and RAST results increased as the skin test score rose. When the skin test was 4+, more than 80% of the Quidel and 60% of the RAST results were positive.

Based on the assumption that all 132 patients were atopic (see "Patients and Methods") the serologic tests were also analyzed for their screening accuracy for atopy. Of the 132 patients in the study, 120 produced at least one positive Quidel allergy screening result. Two patients were not tested for the Quidel screen, resulting in a screening accuracy rate for atopic patients of 92.3% (120/130). The corresponding rate for RAST was 75% (99/132). If a 4+ skin test was considered the unequivocal criterion of atopy, a subset of 104 patients remained, of which 99 had at least one positive Quidel test. Again, one of these patients was not tested for the Quidel screen, resulting in a screening accuracy of 96.1% (99/103). For RAST, the corresponding rate was 85.6% (89/104).

After completing a brief training session, the nontechnical office personnel had no difficulties doing the procedure. Their results were not significantly different from either those obtained on the same specimens in a double-blind fashion by trained technicians at the manufacturer's laboratory or those obtained when the dipstick color development was analyzed by a photometric device instead of visually.

Discussion

In this study, we compared a new dipstick antibody-based enzyme immunoassay for detecting specific IgE with skin testing and RAST, which are widely used as diagnostic tools. The purpose of the Quidel allergy screen is to provide an easy, rapid, and cost-effective means of screening for allergic disorders in primary care physicians' offices. The test is proposed as an allergy screen and not as a diagnostic tool for initiating a comprehensive, specific treatment program that might include avoidance measures, environmental controls, and immunotherapy. If the screen proves accurate in differentiating atopic from nonatopic patients, it may be used for referring patients for further allergy evaluation and treatment.

The results show that the Quidel screen was more sensitive than RAST (overall 68.5 versus 42.1) in this multicenter trial. The overall higher sensitivity makes the Quidel test a better screening method than RAST if a few selected allergens are used. The sensitivity among the individual allergens varied considerably, possibly because of the differing amounts of allergen-reactive protein coupled to the solid-phase support. The overall sensitivity of the RAST in this study was low (42.1%), making it less suitable for screening. The sensitivity of the RAST is lower in our study than reported elsewhere.[8] One possible reason may be that both intradermal and prick tests were done in our study. Another reason may be that the allergens used in the skin and Quidel tests were more similar than those used in the Phadebas RAST, which were derived from another source. The specificity of the overall nine allergens with the Quidel screen was 64.1%, with variation among individual allergens. The specificity of the nine allergens with RAST was 93.4%, however, which is similar to figures published by others.[9] The data also showed that the higher the specific IgE level based on skin-test responses, the more likely the Quidel and RAST tests will be positive. Although the current sensitivity of Quidel testing used in this study may be acceptable for allergy screening, with further refinements in the procedure technique, specific allergen reactivity may improve the overall accuracy and screening efficacy of the test.

In conclusion, the Quidel allergy screen is a simple, rapid, qualitative in vitro test for specific IgE and may have a place in allergy screening in primary care physicians' offices.

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Book Review

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

Interventional Radiology

Edited by Wilfrido R. Castañeda-Zuñiga, MD, MSc, Professor of Radiology, University of Minnesota Hospital and Clinic, and S. Murthy Tadavarthy, MD, Clinical Assistant Professor of Radiology, University of Minnesota Hospital and Clinic, and Chief, Section of Cardiovascular Interventional Radiology, Abbott Northwestern Hospital, Minneapolis. Williams & Wilkins, 428 E Preston St, Baltimore, MD 21202, 1988. 855 pages, $149.95.

This text is a comprehensive, highly detailed work focused entirely on the practice of interventional radiology. Included are indications, equipment, techniques, and problems that may be encountered in doing virtually any of the imaging-guided interventional procedures. The book primarily is designed for the practicing interventional radiologist, although many of the chapters would be of interest to some of the referring subspecialists. The chapter addressing the mechanism and technique for angioplasty and the chapter on thrombolysis relate directly to the clinical practice of the vascular surgeon. Chapters on percutaneous nephrostomy, ureteral stent placement, and treating varicoceles would interest urologists. Chapters on managing gastrointestinal bleeding and treating pancreatic and hepatobiliary pathology are of value to the gastroenterologist. Chapters on needle biopsy and abscess drainage serve the general surgeon well.

The opening chapter briefly examines interventional radiology from an historical perspective and discusses the future of the subspecialty. The second chapter deals with the important issue of radiation protection when doing interventional techniques. The remaining 29 chapters are generally excellent. Very little is overlooked. Throughout the text there are quality radiographic images and some well chosen histologic sections to illustrate the effects of various therapeutic techniques. A major strength of the book is its liberal use of excellent schematic representations of the techniques described, which facilitates understanding them. The book also includes important information regarding complications and potential pitfalls of various procedures, as well as pre- and postprocedural care for the patient.

Although the text is very broad in scope, some areas are only briefly covered. The section on laser angioplasty is merely an overview, reflecting the development of this technology over the last few years. Similarly, there are no sections about atherectomy or endovascular stents, for the same reason. With the exception of one chapter on treating hepatocellular carcinoma, there is little on the subject of regional therapy for neoplasms. Also lacking are discussions of diagnosing and treating vasospastic disorders of the extremities and gastrointestinal tract, epistaxis, and impotence.

Nonetheless, even considering a few shortcomings, this text is excellent and a notable contribution to the medical literature as a reference source primarily designed for the practicing interventional radiologist.

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Informed Opinion

The Future of Family Practice Training in California

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H. JOHN BLOSSOM, MD, *Fresno, California; and* WILLIAM H. BURNETT, MA, *Sacramento, California*

Although the number of physicians in California has doubled since 1963, the number of family and general practice physicians has declined. The ratio of office-based primary care physicians to population has also decreased. Graduate medical education is funded largely from patient care revenues, but the low rate of reimbursement for ambulatory care makes training in primary care specialties especially dependent on public support. Medicare, the Veterans Administration, and the University of California provide more than $325 million a year in support of graduate medical education in California. Federal and state grant programs provide $5 million a year for family physician training in the state, but appropriations to these programs have been reduced in real terms. California family practice residencies are disproportionately located at county hospitals, where funding shortfalls make them especially vulnerable to cuts in grant programs. Additional resources will be needed if more family physicians are to be trained.

(Midtling JE, Barnett PG, Blossom HJ, et al: The future of family practice training in California. West J Med 1990 Mar; 152:317-321)

It has been two decades since family practice became the 20th American medical specialty. The founders of the family practice movement were concerned about the growing specialization of medicine and the sharp decline in the number of general practice physicians. Of special concern were the needs of rural areas, which were especially dependent on general practice physicians.

Within its first decade the new specialty flourished, and more than 300 residency programs were created nationwide, assisted by special funding from the federal and state governments. Family and general practice physicians now provide 30.5% of the office visits to United States physicians.[1]

In California more than 2,000 family physicians have been trained by the state's 35 residency programs. Most of the state's medical schools have created a department of family medicine, and a few have made family medicine clerkships a mandatory part of their undergraduate curriculum.

Despite this remarkable growth, there is persistent concern that there are too few primary care physicians. In this study we report recent data on the distribution of physicians and the sources of support for their graduate medical education in order to estimate the ability of California residencies to meet the state's need for family physicians.

Physician Distribution in California

California had 8,372 allopathic physicians in 1986 who identified themselves as specializing in family or general practice.[2(p132)] Of these, 85% were office based, 8.6% were in training, and the balance were hospital based or in teaching or administrative positions.

There were an additional 830 osteopathic physicians in the state, most of whom were in general practice.[3(p510)] Most California osteopaths availed themselves of a state law that allowed them to become doctors of medicine, and no new osteopathic licenses were issued in the state between 1962 and 1974. Osteopaths consequently play a smaller role in providing primary care in California than they do in many other states.

Information on the number and the specialty of allopathic physicians has been published since 1963 by the American Medical Association.[4] Between 1963 and 1986, the number of physicians in California increased by 121.3%, while the population increased by only 54.1%.[2] During this period the number of office-based physicians in family and general practice actually declined by 9.6% (Table 1). While the number of general internists and pediatricians increased faster than the population, this did not completely compensate for the decline in the number of family and general practitioners. In 1963 there were 67.5 office-based primary care physicians for every 100,000 California residents, but by 1986 there were only 64.0.

Most of the increase in the number of California physicians has been confined to the ranks of medical, surgical, and other subspecialties and to administrative and hospital-based physicians. Recent data confirm that this trend continues to the present. Over the past five years, the number of office-based family and general practice physicians in the state increased at an average annual rate of 1.9%, compared with a 3.1% annual increase in the total number of California physicians and a 2.2% growth in the state's population.[2,5]

The growth in physician numbers has occurred disproportionately in urban areas, exacerbating the geographic maldis-

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TABLE 1.—*Number of Active, Nonfederal California Physicians, 1963 to 1986, and Ratio Per 100,000 Population**†

	Number			Ratio to Population		
Office-Based Primary Care Physicians	*1963*	*1986*	*Change, 1963-1986*	*1963*	*1986*	*Change, 1963-1986*
General/family practice	7,847	7,095	−752	44.8	26.3	−18.5
Internal medicine‡	2,826	7,053	4,227	16.1	26.1	10.0
Pediatrics§	1,148	3,136	1,988	6.6	11.6	5.1
Subtotal, office-based primary care physicians	11,821	17,284	5,463	67.5	64.0	−3.5
Total active physicians	28,073	62,123	34,050	160.3	230.1	69.8

*From Roback et al[2] and Theodore and Sutter.[4]
†Osteopathic physicians are not included.
‡Figures include all subspecialties except cardiology, gastroenterology, and pulmonary diseases.
§Figures include all subspecialties except pediatric allergy and pediatric cardiology.

tribution of California physicians. In 1963 California counties outside of metropolitan areas had a ratio of 104.1 patient care physicians per 100,000 population, which was 63.1% of the ratio in the major metropolitan areas (counties with a population of more than 400,000). By 1986 the rural physician-to-population ratio increased to 119.1, but this ratio was only 53.6% of that in the major metropolitan counties.

Among the specialties, only family and general practice physicians disproportionately locate in rural counties—the ratio of office-based general and family practice physicians to population is higher in rural counties than in California as a whole. In 1963 the ratio in rural counties was 13.6% higher, and by 1986 it was 23.6% higher. As there were fewer family and general practice physicians in 1986, and because other specialties did not increase their entry into rural areas sufficiently to compensate for this decline, the ratio of physicians to population has grown more slowly in rural California than in the rest of the state. Thus the decline in the ratio of office-based physicians to population has been more severe in rural counties.

The aging of the state's family and general practice physicians will exacerbate the deficit in primary care physicians for at least ten more years. In 1983 more than 3,144 (or 39.9%) of the state's family and general practice physicians were older than 55 years.[6] The 234 family physicians who graduate from California family practice residencies each year are too few in number to replace the family and general practice physicians who will retire in the next decade. Young California physicians are entering family or general practice at rates much lower than their cohorts of 30 years ago (Figure 1).

Although physicians migrate to California from other states, data on residency-trained family physicians suggest that this will probably have little effect on the supply of family physicians. By July 1987, California residencies had trained 2,028 family physicians.[7(p11)] As 2,153 residency-trained family physicians practice in the state, the net immigration was only 125 physicians. It is well documented that physicians are more likely to locate where they completed their residency than where they completed medical school.[8-10] This is especially the case for the graduates of family practice residencies.[11]

The California Health Manpower Plan reports that despite an overall surplus of physicians in the state, there is a shortage of primary care physicians.[12] The plan relates that 36 of the state's 58 counties have fewer primary care physicians than are needed to meet even the lowest standards of adequacy (83 per 100,000 population). This shortage is especially acute in rural areas. The plan also identifies a number of poor urban communities that have too few primary care physicians.

This problem is not restricted to California. The Council on Graduate Medical Education recently reported that the nation has a shortage of family physicians, even though there is an aggregate oversupply of physicians.[13(p18)]

Support for Graduate Medical Education in Family Practice

Information on public support for graduate medical education in California was obtained from state and federal agencies. Information on the number and specialty of residents being trained was obtained from the California Office of Statewide Health Planning and Development, the Veterans Administration, the American Medical Association, and the American Academy of Family Physicians. Unless otherwise stated, all data are for the 1985-1986 academic year.

The rapid growth in family physician training programs that characterized the 1970s is over. There were an average of 703 family practice residents in California in each of the last seven years, with their number varying by as much as 3% from this figure. The 728 family practice residents in training

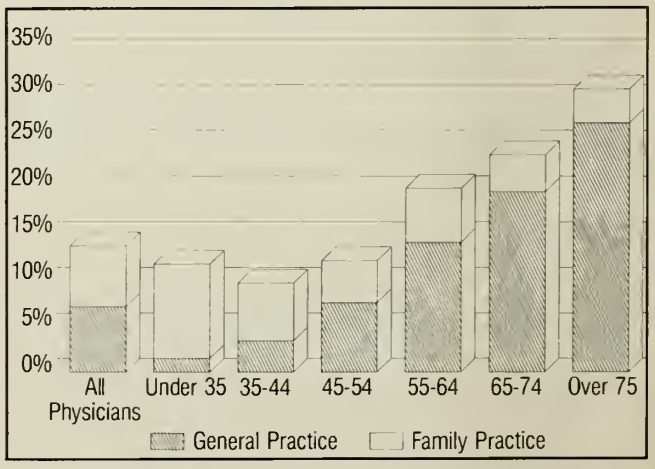

Figure 1.—The graph shows the percentage of California physicians in family and general practice during 1983 by age cohort.

during the 1988-1989 academic year represent 9.1% of the state's resident physicians.

The distribution of family practice residents among teaching hospitals differs from that of other specialties. Family physicians are more likely to train in hospitals operated by county governments, nonprofit corporations, and the US Department of Defense and are less likely to train in hospitals operated by the Veterans Administration or the University of California (Figure 2). Because public support for graduate medical education is not provided uniformly to all hospitals, this distribution affects the funding of family physician training.

The costs of graduate medical education are paid primarily from patient care income. The Council of Teaching Hospitals reports that its members meet 81% of the cost of resident stipends from patient care revenue.[14] Because family practice residents undertake relatively few procedures and spend much of their time in the outpatient setting, they are much less able to generate patient care income than are the procedurally oriented, inpatient-based specialties. It has been estimated that more than a third of the costs of family practice residencies must be met from sources other than patient care income or hospital support.[15] This remaining support consists chiefly of public funds.

Federal Funding

Federal support for graduate medical education is provided through several different programs. These include Medicare payments to nonfederal hospitals, resident stipends paid by the Veteran's Administration and the Department of Defense, and funds granted pursuant to Title VII of the Public Health Service Act.

Medicare paid US hospitals $3 billion during the 1987-1988 fiscal year for the costs of graduate medical education.[16] A third was in reimbursement for direct costs, and the balance consisted of the indirect medical education payment, paid in recognition of the higher patient care costs incurred by teaching hospitals. With 9.4% of the nation's residents, California's share of Medicare education payments was approximately $290 million.

The indirect payment to hospitals varies with the intensity of teaching. Teaching intensity is defined as the ratio of residents to hospital beds. Family practice residencies tend to be located at hospitals with a lower teaching intensity. The nonfederal hospitals in California with family practice programs had a resident-weighted average of 0.238 residents per bed. The resident-weighted average for teaching hospitals that do not train family physicians was 0.363 residents per bed. These ratios translate to an 18.1% indirect costs rate for family practice and a 26.7% rate for other specialties. Rates are multiplied by a hospital's Medicare prospective payment to determine the indirect costs reimbursement.

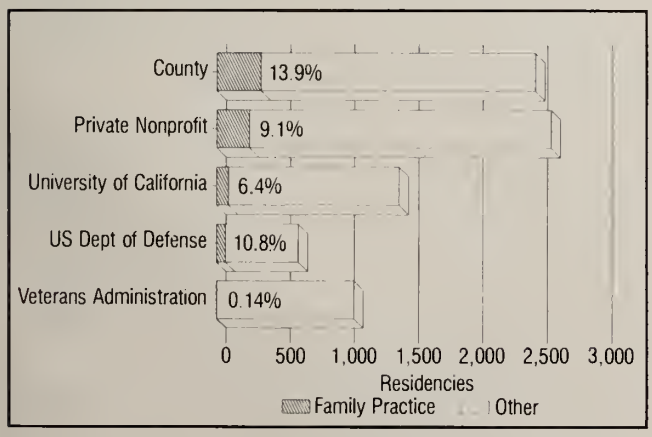

Figure 2.—The graph shows the distribution of resident physicians among California hospitals in 1985, according to hospital ownership category, with the percentage of residents training in family practice.

This differential between family practice and other specialties is partially compensated for by the slightly greater portion of patient days spent by Medicare patients at hospitals with family practice programs. They have a resident-weighted average of 28.2% Medicare days compared with 24.0% for all other specialties.

Medicare patients who are enrolled in health maintenance organizations are excluded from the calculation of the graduate medical education payment. This is likely to have a greater effect on community hospitals, which disproportionately train family physicians, and much less effect at multispecialty teaching hospitals where tertiary care services are rendered outside of capitated plans.

The stipends of residents who train at hospitals operated by the Veterans Administration and the Department of Defense are paid by federal funds. There are 1,069 residency positions at Veterans Administration hospitals in California, or 12.9% of the residency positions in the state. The Veterans Administration spends an estimated $24.3 million a year for the stipends of these residents. Most positions are occupied by a succession of residents on rotation from programs based at other hospitals. Only 1.5 (0.14%) of these positions is in family practice.

Another 636 residency positions (7.6% of the state total) are at hospitals operated by the Department of Defense, with an estimated stipend support of $14.5 million a year. Family practice residents occupy 69 (10.8%) of these positions.

The Public Health Service awarded $20.2 million in training grants to family practice residencies in the United States in 1988. The family practice grants have declined by 35.7% in absolute dollars since 1978 and by 63.8% in inflation-adjusted dollars. A total of $2.6 million was awarded to 20 California family practice residencies in 1987, down from $3.1 million granted in 1984.[17]

Federal funds administered by California's Area Health Education Centers provided $3.5 million in program support to family practice residencies during the seven years between 1980 and 1986. Federal funding of this program ended on September 30, 1988.

State Funding

Most state support for medical education is provided through appropriations to the medical schools of the University of California. The University of California Division of Health Sciences received a $276.4 million appropriation in the 1988-1989 fiscal year, a nominal increase of 107.2% over 1979-1980 funding and a real increase of 39.5%. Most of this appropriation is used for undergraduate medical education.

The state appropriation to the University of California is determined in part by the number of "budgeted residents" in training at all hospitals affiliated with university medical schools. Of 4,159 residents, 36.9% trained at hospitals oper-

ated by the university and 63.1% at hospitals affiliated with it. Family practice residents are less likely than other residents to train at University of California hospitals. They account for 6.5% of the residents at university-operated hospitals and 15.1% of the residents at affiliated hospitals.

The state does not require the University of California to allocate funds among the hospitals or specialties in proportion to resident numbers, and it does not. The contribution that state support of the university made to the graduate training of family physicians was obtained by surveying deans of the five University of California medical schools and the staff of the departments and divisions of family medicine in these schools.

State funds are used to pay 40% of the stipends of residents at hospitals operated by the University of California. Of the $13.1 million in stipend support, $899,000, or 6.8%, supported family practice residents at these hospitals.

Another $136.5 million was spent by departments in the five medical schools. The university allocated $3.1 million, or 2.2%, to its five departments and divisions of family medicine. Because faculty members teach both medical students and residents, it is not possible to determine what portion of these funds are used for graduate medical education.

In 1982 the state legislature reduced funding for graduate medical education at the University of California but directed the university to maintain the number of family practice resident positions.[18] Because the university does not control the size of residency programs at its affiliated hospitals, it did not have the means to implement this directive.

The state also supports the training of family physicians through the California Family Physician Training Act, also known as the Song-Brown Act. The Song-Brown program received $2.88 million in fiscal year 1988-1989, a decline of 1.6% since 1979-1980, or, in real terms, a reduction of 33.8%. About 80% of the Song-Brown funds go to family practice residency programs. Grants are given to residencies that have increased their size, with priority given to those programs that can show a history of training physicians who practice in the medically needy areas of the state. The state budget for 1989-1990 proposed eliminating all funding to the Song-Brown program. In response, several family practice residency programs developed plans to reduce their program size and range of activities. Funds for 1989-1990 were eventually appropriated, but future funding is not certain.

Local Government Support

County hospitals are where 45.3% of California family practice residents train. Only 28.3% of the residents in other specialties are at county facilities. Many of the county-based family practice programs grew from long-established general practice residencies. Severe underfunding of county hospitals is affecting family physician training. A county hospital that was the principal site of a family practice residency program closed in 1988. During the past five years financial pressures have caused ten other California county hospitals to consider terminating their family practice residency as a means of economizing.

Discussion

The shortage of family practice and other primary care physicians is a serious problem facing the health care system that must be addressed by medical educators and public policy makers. The shortage of primary care training positions has been aggravated by the fact that graduate medical education in the United States has become increasingly reliant on patient care income. The relatively low levels of reimbursement for the ambulatory and cognitive services that are characteristic of family practice make it impossible for family practice residencies to become entirely self-sufficient. Both the Council on Graduate Medical Education and the Graduate Medical Education National Advisory Committee found that the training of physicians in the primary care specialties, including family practice, needs greater subsidy than other specialties.[19]

Congress and the California legislature have funded family practice residency grants programs that have helped improve the geographic and specialty distribution of physicians. Despite a persistent and growing shortage of family physicians, these programs are faced with cuts or elimination. Many family practice residencies in the state are now finding it difficult to persevere, let alone expand. The tenuous status of the state grants program poses a serious threat to their viability.

The California legislature has sought to influence the specialty mix of physicians through the University of California budget. This effort has not succeeded, however, as most family physicians do not train at hospitals operated by the University of California. The state of California could more effectively encourage family physician training by maintaining and even augmenting appropriations to the California Family Physician Training Act program, as these monies support programs at University of California hospitals as well as other hospitals.

Congress should augment its appropriations for family physician training and restructure the formula for calculating Medicare medical education payments to reflect the nation's need for the specialty of the physicians being trained. Implementing the resource-based relative value scale would more fairly compensate primary care physicians for cognitive services and may provide increased patient care revenues for family practice residency programs.

Medical educators have some power to resolve the undersupply of family physicians. Medical schools with full departments of family medicine and those with required family medicine clerkships are more likely to produce graduates who choose family practice as their specialty.[20,21] Without new funding initiatives, however, it will be difficult for medical educators to address societal concerns regarding the shortage of primary care physicians.

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Nicotine Gum to Help Patients Quit Cigarettes

NICOTINE GUM is pretty safe. You should not, however, give it to people who have had a myocardial infarction in the last three or four months or who have serious arrhythmias because some people, despite your instructions, do chew and smoke at the same time. And they can get incredibly high peak levels of nicotine that may precipitate arrhythmias. Never prescribe the gum for pregnant or nursing patients. If patients use it correctly, they can avoid many of the common side-effects—sore jaws and mouth, heartburn, hiccups, dizziness. The heartburn and nausea, we think, are largely due to the swallowed nicotine. There is no reason to swallow it. They can, in fact, spit it out if they are in a position where they can do that without offending company. The sore jaws and mouth come from chewing too vigorously.

If patients are going to use nicotine gum, I would suggest that they first set a date to quit smoking. We find many physicians give out nicotine gum because the patient comes in and asks for it. "Doc, can I have a prescription for nicotine gum?" And they say, "Okay, sure, here's your prescription," and walk away. And the patients expect that if they chew the gum, they are going to quit smoking. It does not work quite that way. Nicotine gum does not cause patients to quit; it only helps *after* they quit. And, therefore, we have come up with a slogan: if a patient asks you for nicotine gum, you ask them for a date. And only those who agree to set a quit date should get nicotine gum—to start after the date.

How long should they use the gum? It is controversial, but at least three months—the manufacturer says six to twelve months is okay. And I think that some might argue that long-term use of nicotine gum in those who are not smoking—very long-term use—is better than returning to cigarettes.

—STEVEN R. CUMMINGS, MD

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Lessons From the Practice

Two Generations—Reflections on Changes in the Treatment of a Chronic Disease

LUCY M. OSBORN, MD, *Salt Lake City*

1962—I was 16 years old when my mother became ill, although illness hardly seems the correct word. My parents and I were taking a short trip to watch Army play Michigan. I first realized something was wrong when we stopped for lunch. As we walked to the restaurant I noticed my mother was limping. Later, returning to the car, she stumbled. When I asked her about it, she shrugged her shoulders and said that her leg was not moving right, she must have slept on it wrong. She seemed nonchalant about it, as if it were not an unusual occurrence.

Two days later, she went to see our small town general practitioner. He diagnosed her as having Guillain-Barré syndrome, a name that meant nothing to us. We understood neither what it was nor what it meant. He told us that it was a reaction to a flu shot she had been given and that there was no treatment. She was ordered to stay in bed for a month.

I now know that she was frightened, but I did not recognize it then. She was outwardly calm and quite stoic. None of us knew what to do, and no one helped us find out. My father was even more frightened. Ignorant of the disease or what might happen, he had no idea what to say or how to be supportive. He left on a short hunting trip, an action he still regrets.

Confined to bed, she slowly became weaker, losing much of the use of her right hand. Her face drooped and her vision blurred. She had difficulty writing; it was hard for her to read. It must have been awful, lying there with nothing to do except to be worried and bored, but she never complained. Later, she did seem to get better, but she never fully regained the function of her right leg. She had always been an athletic, active woman, and I knew the impairment bothered her.

After a year or so, my parents decided to seek another opinion, traveling to a major university medical center to see a specialist. They were told that, indeed, she had had a reaction to the flu shot but that the name of the problem was demyelination syndrome. This name, as with the first, meant nothing to us, but the prognosis did: There was nothing that could be done; physical therapy would be useless. She just had to learn to live with her limitations. She seemed to. As time went on, to those of us who lived with her, it seemed a nuisance, not a disease.

Several years later, when my father retired from his business, my parents were denied an application for health insurance. The insurance company refused to give a reason for the denial. My parents were quite puzzled because, to their perception, they were both healthy, sturdy midwesterners. They finally concluded that it had to be related to my mother's hospital evaluation.

I was then a junior medical student at the institution where my mother had been seen. My father asked if I could check her medical record for an explanation. Unconcerned, I walked to the medical records department and requested my mother's chart. Within five minutes I was holding the folder. It seemed odd to see now-familiar phrases describing my mother: "This attractive 45-year-old woman enters the hospital for evaluation of neurologic deficits." I had never stopped to consider that someone might think my mother attractive, and I certainly had not thought of her as having "neurologic deficits." I scanned the description of the physical examination: "Horizontal nystagmus, weak extensors in the right leg, foot drop, increased deep tendon reflexes, loss of sensation in several areas, positive Romberg, positive Babinski . . . multiple, scattered neurologic deficits." There were some laboratory results. I turned to the last page. Final diagnosis: multiple sclerosis. I was incredulous. I had not thought about my mother's problems since entering medical school, but certainly in retrospect the diagnosis made sense. It obviously was not Guillain-Barré syndrome. Had that been ignorance on the part of our family physician, or had he been afraid to give an honest diagnosis? Why hadn't the neurologists told her?

I was not sure what I should say to my parents but finally decided that there was nothing to do except report what I had read. My mother's reaction was straightforward: She didn't believe it. The doctors had told her that she had "demyelination syndrome." If she had had multiple sclerosis, they would have told her. That was why she had sought their opinion.

1985—More than two decades after that trip to Michigan, my husband and I took a weekend vacation with our children. I found I could not run on the beach. I kept stumbling; I had a foot drop. Like my mother, I ignored it: I must have slept on it wrong. I did not mention it to anyone, and no one else noticed. Several months later, I finally went to see my internist. I had bothersome paresthesias, odd vibrations that roamed my body each time I looked down. After his examination, he told me that it was probably nothing but wanted me to see a neurologist the following day.

Denial is a strong emotion. I was not worried in the least, just curious about these odd, varied symptoms. I had had many others over the past several years but found a conve-

(Osborn LM: Two generations—Reflections on changes in the treatment of a chronic disease. West J Med 1990 Mar; 152:322-323)

From the Department of Pediatrics, University of Utah Medical Center, Salt Lake City.
Reprint requests to Lucy M. Osborn, MD, Department of Pediatrics, University of Utah Medical Center, 50 N Medical Dr, Salt Lake City, UT 84132.

nient explanation for each, never thinking them worthy of mention. As the neurologist examined me, I found I could not walk toe-to-heel; as I closed my eyes, I fell over; I could not feel the tuning fork, nor the pinpricks . . . multiple, scattered, neurologic deficits. Yes, I, like my mother, have multiple sclerosis. But here, our tales diverge.

After the examination, the neurologist sat down, looked at me, and said, "I could beat around the bush, or I could just tell you what's wrong. I know the best course is simply to tell you the truth. You've got multiple sclerosis." A magnetic resonance scan left no questions about the diagnosis. A spinal tap confirmed active disease.

Unlike my parents before me, I was offered not only a diagnosis but, with my husband, also given a detailed explanation of the disease. The neurologist—correctly—did not assume that we would know about multiple sclerosis, despite the fact that we are both physicians. Our stress and emotional response to the disease were not ignored. We were informed about support groups and advised to get counseling. With our psychologist we were able to discuss our fears, share our concerns, and together face a disease that at least has a name, if an unpredictable course. Ironically, my husband also went hunting, not in ignorance, as my father had, but as an escape from a frightening, puzzling situation.

The neurologist helped us again. He would call my department chairman if I wished. It was unnecessary, for we made another decision that has been a blessing: not to hide the diagnosis from either friends or colleagues. I finally told the residents I supervise and received an amazing response: "Thank goodness it's only that. You were so pale and seemed so stressed. We knew something was wrong. We were all worried you had leukemia!" The conspiracy of silence that so often in the past, and still today, surrounds the diagnosis of a chronic disease produces more fear and anxiety than knowledge of the disease possibly could.

I was not put at bedrest but encouraged to exercise. I stayed active, but the disease gradually progressed. When walking became difficult, I was again offered something not possible for my mother—treatment. After a short course of immunosuppressants, I was amazed and delighted to awaken one morning and find that I could wiggle my toes. Several days later I could flex my foot, then gradually I regained strength in my leg. A month later I discarded my cane and have not used it since. Physical therapy helped me compensate for lost muscles and strengthen weak ones.

My mother grieves that I have this disease, for she has lived with the handicaps. Yet, I can bicycle and ski. She, who is now 70, still plays golf but cannot walk without assistance. As I watch her struggle from living room to kitchen, I grieve for her, for the opportunities I have had that she did not. What would have happened had she known what afflicted her? What if she had been given a fitness program and physical therapy? How much more functional could she be today? Counseling or a support group could have helped my parents face a frightening event and a chronic disability. She was given hopelessness; I have been given hope.

It is my prayer that my mother's treatment is something of the past; it is my fear that it is not. Not all patients are blessed with the medical care I have received. Nor do many people who are chronically ill have colleagues who understand their condition, who can be supportive at work and help them to remain as functional as possible. Giving medications is the easiest part of any treatment. Thinking of the patient's life is more difficult—counseling the patient on how to approach the disease with friends, family, and colleagues, marshalling the support of psychologists, physical therapists, other specialists, referring patients to support groups—this takes time, effort, and compassion.

I don't know what my future holds, but, then, neither does anyone else. I simply have a name to attach to the uncertainty. There is one fact, however, that is assured: The quality of my life will be better than my mother's. I have had physicians who do more than give me a pill, who see me as a person, not just as a case of multiple sclerosis. They have remembered my health, not just my disease. Although it has been said a thousand times, I want to say it again. Please, treat the patient, not the disease. Though the disease may be incurable, the patient is not.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

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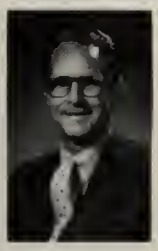
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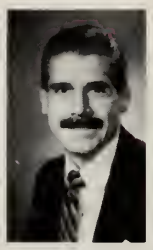
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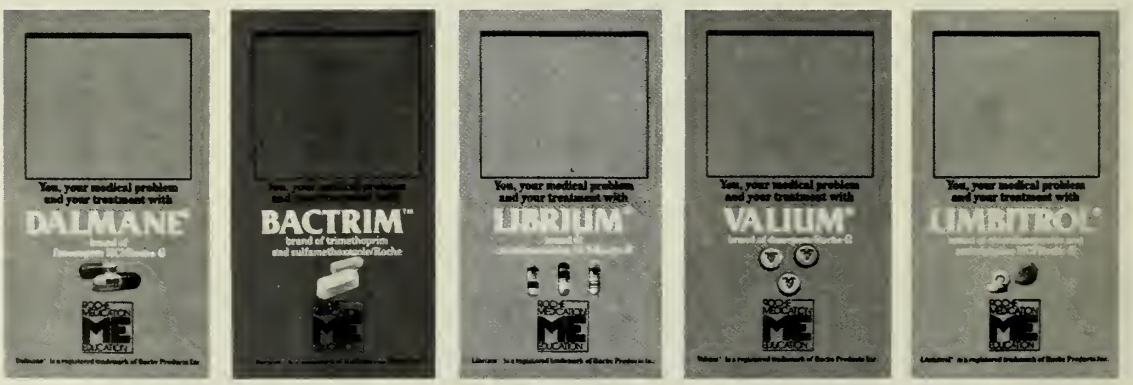

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CALIFORNIA MULTISPECIALTY. Cardiologist, Anesthesiologist, Infectious Disease Specialist, Internal Medicine, Pediatrician, Endocrinologist, Orthopedist, General/Family Practitioner, Obstetrician/Gynecologist, Pathologist, General/Thoracic Surgeon, Gastroenterologist. Excellent opportunity for physicians in Los Angeles suburb to join 100 member multispecialty medical group. Large fee-for-service and prepaid practice, no Medi-Cal. Excellent compensation program based on guarantee plus incentive, profit sharing and pension plan. Group provides health, dental, life, and malpractice. Partnership in real estate and medical corporation available. Send CV to Ron McDaniel, Assistant Administrator, Mullikin Medical Center, 17821 S. Pioneer Blvd, Artesia, CA 90701.

WANTED: BC/BE FAMILY PRACTICE OR INTERNAL MEDICINE/PEDIATRICS with Emergency Medicine experience for second physician in our Emergency Department. ACLS/ATLS required. Boise offers a variety of cultural activities and is close to skiing, hunting, fishing, white water. Contact Idaho Emergency Physicians with CV at 2312 N. Cole Rd, Ste B, Boise, ID 83704.

SOUTHERN OREGON. BC/BE Family Practitioner to join busy five doctor Family Practice group summer 1990. Practice is located in the Rogue Valley, which is amply endowed with cultural events and outdoor activities. Affordable housing in area of low seismic potential. Admission privileges available at two local hospitals. OB optional. Guaranteed salary and benefits with option to join group after one year. Send CV to Daniel Heyerman, MD, Central Point Medical Group, PC, 524 Manzanita, Central Point, OR 97502.

CALIFORNIA, NORTHERN. A stable group of four ABEM certified/eligible MDs at coastal hospital of 24,000 patient visits would like two new associates. Income $60-$75 per hour. Will consider Family Practice but prefer Emergency Department trained Emergency Physician. Coastal paradise near redwood national parks, minutes from Klammath, Rogue, and Smith Rivers. Video tape of area available. Send CV to EPMG, 120 Montgomery St, Ste 1000, San Francisco, CA 94104.

(Continued on Page 330)

The Permanente Medical Group
Northern California

Quality

Stability

Leadership

Growth

Support

Rewards

The Permanente Medical Group, the largest multispecialty group practice in the U.S., is undergoing explosive growth in its Northern California region: the San Francisco Bay Area, Sacramento and the Central Valley. Our rapid increase in membership has created practice opportunities throughout the region.

Our physician-managed group is part of the comprehensive Kaiser Permanente Medical Care Program. As a TPMG physician, you have access to the latest medical technology and resources, the support of colleagues in all subspecialties — and the opportunity to provide excellent health care without the burdens of managing a practice.

Join us in one of these facilities:

- Walnut Creek/Pleasanton
- Martinez/Antioch
- Oakland
- South Sacramento/Stockton
- Santa Rosa
- San Jose/Gilroy
- San Francisco
- South San Francisco
- Sacramento/Roseville
- Richmond
- Redwood City
- Fresno
- Hayward/Fremont
- Santa Clara/Milpitas/Sunnyvale
- Vallejo/Fairfield/Napa
- San Rafael/Petaluma

TPMG offers many benefits: scheduled time off with cross-coverage provided by your colleagues, continuing education, malpractice insurance, a substantial retirement program and special arrangements for physicians transferring from established practice. For complete information, call or send CV to: The Permanente Medical Group, Inc., Richmond Prescott, M.D., Physician Recruitment Services, Dept. WJM-7155, 1814 Franklin, 4th Floor, Oakland, CA 94612. (800) 777-4912. EOE

KAISER PERMANENTE
Good People. Good Medicine.

(Continued from Page 328)

Longview is a picturesque, stable community of 42,000 located near the Columbia Gorge and the coastal mountains and beaches of Washington and Oregon. Members of our 12 physician group enjoy individual subpractices, infrequent call, and excellent facilities in our new clinic. We invite you to contact us regarding practice opportunities.

SALT LAKE CITY, UTAH, FAMILY PRACTICE PHYSICIAN, BC/BE. Excellent opportunity in Salt Lake suburb to join busy practice, near excellent skiing, hunting, and fishing. Our clinic operates six days a week, and our patients are from a growing Salt Lake suburban population. Excellent salary and benefits. A partnership opportunity will be available after two years. Send CV to Robert Davis, MD, Director, Family Medical Center, 1781 W. 90th S., West Jordan, UT 84092; (801) 562-9100.

SACRAMENTO AMBULATORY / URGENT CARE. Family Practitioners/Internists needed to staff adult urgent care center in Sacramento. Part-time shifts available. Clinic operates seven days per week, 12 hours per day. Excellent hourly remuneration. Benefits possible. Contact Stuart Hahn, MD, (916) 973-5546, or request application from Carolyn Whelan, Physician Recruiting, The Permanente Medical Group, Inc, 2025 Morse Ave, Sacramento, CA 95825. EOE.

RADIOLOGIST. Immediate opening for BC General and Diagnostic Radiologist at teaching hospital near Seattle. Ultrasound, CT, and mammography, plus limited basic angiography and interventional skills. Washington license not required. Regular hours. Full-time or six to nine months per year. Five-year contract. Call Dr Bernstein, (206) 840-9652.

CENTRAL CALIFORNIA. Join our team of Family Practice Physicians in a progressive community health center near Fresno, California. Competitive salary with extra on-call and overtime. Malpractice paid. Generous vacations and time-off policy. Affiliated with UCSF with on-site Family Practice residents and medical students. Varied practice, including Obstetrics, Pediatrics, and in-patient care with an emphasis on health maintenance, patient education, and primary care research. Position is 60 percent clinical, 40 percent teaching. Bilingual English-Spanish helpful. Contact Ardeth Bier, Fresno County Dept of Health, PO Box 11867, Fresno, CA 93775; (209) 445-3353.

URGENT CARE PHYSICIAN. Full- or part-time position available for northern California urgent care clinic. Contact David Lyons, MD, 900 Oro Dam Blvd, Oroville, CA 95991; (916) 534-9183.

GASTROENTEROLOGIST — SAN DIEGO. Thriving multispecialty private practice group seeks Gastroenterologist. The practice offers excellent opportunity to enjoy growing group, see private and managed care patients and build stable future. Compensation includes guarantee plus incentives and benefits. Please send CV to Miriam Stephens Drake, 1450 Frazee Rd, Ste 605-1, San Diego, CA 92108; or call (619) 295-0599.

WASHINGTON STATE
ROCKWOOD CLINIC, PS

An expanding 65 physician multispecialty fee-for-service group seeks BC/BE physicians in the following specialties:

- ALLERGY
- CARDIOLOGY
- DERMATOLOGY
- INTERNAL MEDICINE
- PEDIATRICS
- FAMILY PRACTICE—permanent, part-time, locum tenens
- GASTROENTEROLOGY
- HEMATOLOGY/ONCOLOGY
- OB/GYN
- RHEUMATOLOGY
- GENERAL SURGERY
- ORTHOPEDICS

Attractive benefit package includes competitive salary leading to early shareholder status.

CONTACT: **Colleen Mooney, Recruitment Coordinator**
Rockwood Clinic, PS
E. 400 Fifth Ave
Spokane, WA 99202
(509) 838-2531

COME ENJOY SPOKANE'S QUALITY LIFE-STYLE!

PUBLIC HEALTH PHYSICIAN

The City of Long Beach is currently accepting applications for the position of Public Health Physician. The successful candidate will be responsible for supervising and coordinating the Health and Human Services Department's delivery of Communicable Disease and Preventive Medical Services, supervising and coordinating professional activities within the department, and contracts with physicians to provide disease control and community health services. The salary range is $2,625 to $9,450 monthly. Appointment will likely be made at $5,500 to $6,420 per month. Starting salary dependent upon qualified training and experience. To apply: possession of a valid physician's surgeon's certificate issued by the California Board of Medical Quality Assurance. Certification or eligibility for certification in one of the medical specialties recognized by an American Specialty Board *OR* three years of experience as a physician in a public health agency (possession of a Master's degree in Public Health or a closely related field may be substituted for two years of public health agency experience). For more information contact:

City of Long Beach
Civil Service Commission
333 W. Ocean Blvd, 7th Floor
Long Beach, CA 90802
(213) 590-6202

AA/EOE

SAN FRANCISCO BAY AREA. BE/BC Internist. We currently are seeking highly qualified Internists and subspecialists to complement our energetic Internal Medicine team. Department members provide a full range of medical services for a population of over 200,000 prepaid Health Plan members. Recently renovated and expanded medical center facilities are within convenient commuting distance to virtually any bay area city and the extensive cultural and recreational activities of northern California. As part of our large, multispecialty group practice, you would enjoy an excellent salary, generous fringe benefits, a flexible schedule, and the opportunity for academic affiliation with prestigious local institutions. Send CV to Winslow Wong, MD, Attn: Administration, Kaiser Permanente Medical Center, 27400 Hesperian Blvd, Hayward, CA 94545. EOE.

SACRAMENTO KAISER PERMANENTE. BC/BE Family Practitioners needed to join large group of Family Practitioners providing ambulatory and inpatient care in a large prepaid health plan. Excellent working environment with strong specialty support. Outstanding financial package. Sacramento is a growing metropolitan area with good schools and recreational activities. Close to San Francisco and Lake Tahoe. If interested, please contact Stuart Hahn, MD, The Permanente Medical Group, Inc, 3240 Arden Way, Sacramento, CA 95825; or call (916) 973-5546. EOE.

PHYSICIAN OPPORTUNITIES NATIONWIDE

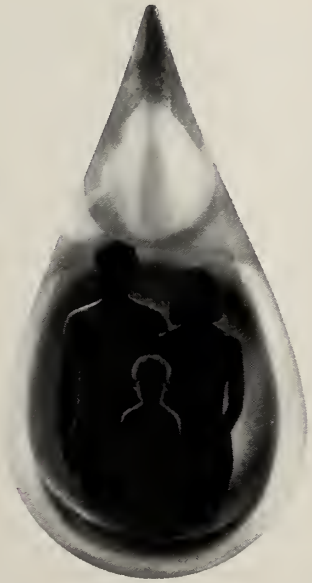
For all specialties for hospitals, clinics, multispecialty groups, partnership and solos. Contact Jim Grant in complete confidence at the bay area specialists, **Nugent & Grant, Inc, 1400 Coleman, Ste B-22, Santa Clara, CA 95050; or call (800) 727-2478, FAX # (408) 727-7390.** Never a fee to the physician.

(Continued on Page 332)

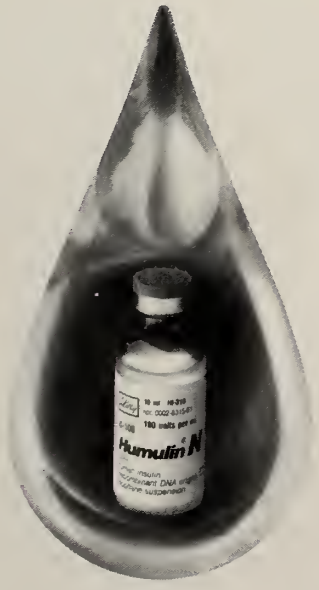
For treatment of diabetes:

Introducing
Humulin® 70/30
70% human insulin isophane suspension
30% human insulin injection
(recombinant DNA origin)

REPLACE
Human Insulin



With Human Insulin



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(recombinant DNA origin)

Any change of insulin should be made cautiously and only under medical supervision.

Lilly
Leadership
In Diabetes Care

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(Continued from Page 330)

R2, R3 POSITIONS, INTERNAL MEDICINE, LDS HOSPITAL, SALT LAKE CITY, UTAH

An additional R2 position and R3 position are now open in the Internal Medicine Residency Program at LDS Hospital. LDS Hospital is a 520-bed fully accredited teaching hospital affiliated with the University of Utah Medical Center. This is an excellent opportunity for talented individuals to experience a high quality Internal Medicine program in beautiful Salt Lake City, Utah. Positions available July 1, 1990. Write or contact Shauna Bruun, House Staff Coordinator, LDS Hospital, Eighth Ave and C St, Salt Lake City, UT 84143; (801) 321-1077. Equal Opportunity Employer.

CITY OF LOS ANGELES PHYSICIAN I $6,446 PER MONTH

Staff physician to care for city employees. Duties include pre-placement evaluations, environmental surveillance exams, and treatment of injured employees. Good knowledge of ambulatory adult medicine is essential. Pay bonus for BE/BC. Full- and part-time opportunities. Forward résumés to: **Dr Goldberg; 1401 W. Sixth St, Los Angeles, CA 90017; or call (213) 485-4641.**

An EEO/AA Employer

GENERAL INTERNIST, BC/BE, needed for a position with suburban satellite clinic of a Seattle area, multispecialty group practice. Diverse patient population includes managed care, fee-for-service, retired and active military. Competitive salary and excellent benefits. Contact Mary Anderson, Pacific Medical Center, 1200 12th Ave S., Seattle, WA 98144; (206) 326-4111.

GENERAL INTERNIST. Steinbeck country, BC/BE General Internist to join dynamic group; includes hospital care, shared call. Spanish helpful. Many visiting consultants, good guarantee with chance for early partnership. Many fringes. One hour to Monterey, three hours to San Francisco. Call or write Helen Poole, 210 Canal St, King City, CA 93930; (408) 385-5471.

URGENT CARE/PRIMARY CARE PHYSICIANS for over 90 positions available with various physician groups in Phoenix metropolitan/Tucson, Arizona. Excellent compensation and partnership opportunities. Contact Mitch Young, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

PUGET SOUND. BC/BE Family Practitioner needed to join three other well established young Family Practitioners in successful half-time practice 30 minutes from Seattle. Strong Family Practice community. Excellent consultant relationships. Obstetrics optional, but preferred. Beautiful area with ample recreational and cultural opportunities. Contact Dan Goodman, MD, 1111 Pacific Ave, Everett, WA 98201; (206) 259-7255.

NORTHERN CALIFORNIA—SAN FRANCISCO BAY AREA. Leading HMO is seeking BC/BE physician to staff a busy urban, full-service Emergency Department with the possibility of administrative advancement. Kaiser Permanente is a large pre-paid HMO offering competitive salary, job security, shareholder status, and generous benefits including health care, life insurance, disability insurance, sick leave, mortgage assistance, and educational leave. Please address all inquiries to David Witt, MD, Emergency Dept, Kaiser Permanente Medical Center, 1200 El Camino Real, South San Francisco, CA 94080-3299; or call (415) 742-2516. EOE.

CALIFORNIA

Primary Care Physicians and Radiologists needed to work as *locum tenens* statewide. High salary, paid malpractice. Work whenever and wherever you wish. Permanent placements as well. **Western Physicians Registry: Northern California, contact Carol Sweig or Jim Ellis, Directors, (415) 673-7676 or (800) 437-7676. Southern California, contact Tracy Zweig, Director, (818) 999-1050 or (800) 635-3175.**

ARIZONA. Established Emergency Medicine group has immediate openings for full- or part-time BC/BE physicians seeking career opportunity in busy Emergency Department with excellent location and case mix. Flexible schedules, excellent living and working conditions. Compensation range $150K to $200K for full-time. Send CV in confidence to General Manager, PO Box 80412, Phoenix, AZ 85060-0412.

FAMILY PRACTITIONER. Steinbeck country, BC/BE Family Practitioner to join dynamic group; includes hospital care, shared call. Spanish helpful. Many visiting consultants, good guarantee with chance for early partnership. Many fringes. One hour to Monterey, three hours to San Francisco. Call or write Helen Poole, 210 Canal St, King City, CA 93930; (408) 385-5471.

CALIFORNIA—NORTH SAN FRANCISCO BAY AREA. Excellent opportunity for BC/BE Family Practitioner to join our growing department in Fairfield. Multispecialty clinic emphasizing personalized care. Full hospital privileges including ICU/CCU, but no Obstetrics. Very favorable call schedule. Prepaid HMO practice provides excellent salary, benefits. Forward CV to Steven Freedman, MD, Kaiser Permanente, 1650 Gateway Blvd, Fairfield, CA 94533; (707) 427-4260. EOE.

FAMILY PRACTICE PHYSICIAN. Full-time in a busy walk-in medical clinic. Located in Visalia, California (Tulare County). Malpractice insurance, good salary, etc. Please call (209) 627-5555 for more information.

SAN DIEGO. Well established multispecialty group composed of Family Physicians, General Internists, OB/GYNs, Pediatricians, General Surgeons, ENT, and Ophthalmologist is expanding. Those interested in joining a vital private practice group, with emphasis in primary care and seeing fee-for-service and managed care patients, are welcome to send CV to Miriam Stephens Drake, 1450 Frazee Rd, Ste 605-1, San Diego, CA 92108; (619) 295-0599.

PHYSICIAN ADMINISTRATOR
Southern California

CIGNA Healthplans of California—a staff model HMO committed to providing innovative, quality health care to 400,000 members in southern California—is seeking a Primary Care Physician to assume the challenging responsibilities of Physician Administrator at one of our 30 health care centers.

You will maintain an active clinical practice with a proportion of time dedicated to leadership and management of physician and support staff. Qualifications must include Board Certification in a clinical specialty and prior management experience. Excellent compensation and benefit package, including bonus plan.

Call collect or send CV in confidence to:

Robert Harrington, MD
Professional Recruitment Dept
CIGNA Healthplans of California
505 N. Brand Blvd, Ste 400-49
Glendale, CA 91203
(818) 500-6570

An Equal Opportunity Employer

EUGENE CLINIC, EUGENE, OREGON

Dynamic 55 physician multispecialty group with seven locations seeks BC/BE physicians in the following specialties: Family Practice, Geriatrics, Occupational Medicine, Orthopedics, Psychiatry, Urgency Care, Urology. Eugene, attractive university town within 60 mile radius of Cascade Mountains and Oregon coast, offers superlative life-style, fine school system, active and varied cultural opportunities, and unlimited recreation. Qualified candidates send CV and three letters of reference to:

Physician Recruiter
1162 Willamette St
Eugene, OR 97401

OCCUPATIONAL MEDICINE PHYSICIAN

Sandia National Laboratories is a research and development laboratory employing 8,500 individuals. The medical department provides a wide variety of services to these employees including occupational health care, emergency care, and health promotion activities. The department is seeking two full-time physicians BE/BC in Preventive Medicine or primary care specialty. Experience in occupational medicine setting desirable. Salary commensurate with experience and includes competitive fringe benefit package. Interested physicians should send résumé and three professional references to:

Shannon Lytle, Staff Recruiting Coordinator
Division 3531-26
Sandia National Laboratories
PO Box 5800, Albuquerque, NM 87185

NORTHRIDGE OUTSTANDING OPPORTUNITY for Internist with/without subspecialty in San Fernando Valley area of Los Angeles. Very large mixed subspecialty consultative practice in Hematology/Oncology and Internal Medicine. Fee-for-service, PPO, and HMO patient base in small group private practice. Teaching encouraged. Association with possibility of partnership. Available March 1990. Call Lorna, (818) 886-8550.

SOUTHERN CALIFORNIA. 39,000 visit Emergency Department in new hospital in San Bernardino. Base station and separate fast track with opportunity to teach. Opening for director and career Emergency Physicians at $90 per hour. Chance to join prestigious, democratic, academically oriented emergency group with excellent benefits. Contact Art Wong, MD, FACEP. Emergency Physicians Medical Group, 120 Montgomery St, San Francisco, CA 94104; (415) 989-1242.

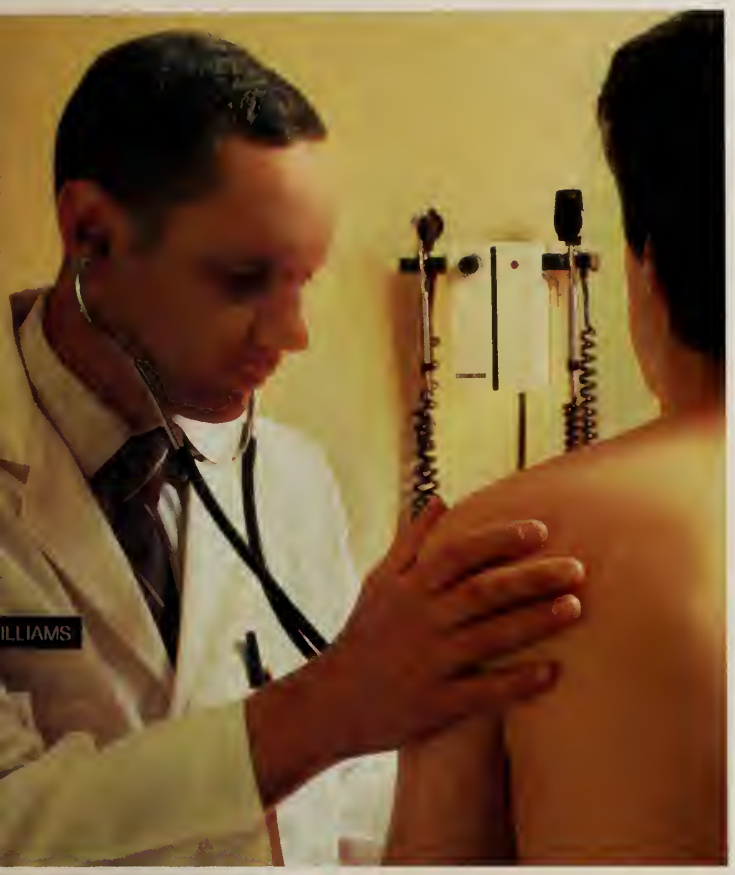
PRIMARY CARE, GENERAL INTERNIST OR FAMILY PRACTITIONER BC/BE to join established Internist in satellite clinic 10 miles from main clinic across state line in Oregon. Main clinic is an expanding 31 physician multispecialty group. Guaranteed income plus excellent benefits. Send CV to Connie Goude, 55 W Tietan, Walla Walla, WA 99362.

RADIOLOGIST—SAN FRANCISCO. Opening for BC Diagnostic Radiologist at Mount Zion Hospital in San Francisco. MR, angiography, CT, ultrasound, general diagnosis. Please contact P. Brodey, MD, 1600 Divisadero St, San Francisco, CA 94115; (415) 885-7466.

LONG BEACH—INTERNAL MEDICINE. BC/BE Internist to join four other Internists in busy primary care practice. Excellent office, lab, x-ray, and support services. Excellent benefits. Send CV to Number 190, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

SOUTHERN CALIFORNIA. Unusual opportunity to take over established orthopedic (medical-legal) practices in east Los Angeles County and/or Orange County. Negotiable terms. (714) 734-3048 or reply to G. Rothman, 417 Associated Rd, A-255, Brea, CA 92621.

(Continued on Page 334)



Airborne training exercise U.S. Army Airborne School

STEVEN C. WILLIAMS, M.D.

Center Medical Director, Health America Corporation, Pittsburgh, Pennsylvania

Captain, U.S. Army Reserve
11th Special Forces Unit, Youngstown, Ohio

EDUCATION University of Connecticut, B.A. with Honors in Biology, Magna Cum Laude
University of Connecticut School of Medicine, M.D.

RESIDENCY Montefiore Hospital, University of Pittsburgh, (Internal Medicine)

OUTSTANDING ACHIEVEMENTS Award for Meritorious Research, University of Connecticut School of Medicine; U.S. Peace Corps Volunteer District Medical Officer, Malawi, Africa; Board of Trustees, First Unitarian Church of Pittsburgh; Secretary, Pittsburgh Area Returned Peace Corps Volunteers' Association; Airborne Qualified.

"My assignment in a Special Forces unit provides an exciting complement to my civilian practice. I've taken courses in rappelling, self-defense, and just completed Airborne School at Fort Benning, Georgia.

"Most of my colleagues think I'm crazy for wanting to jump out of an airplane, but completing the course has given me a great sense of accomplishment.

"Of course, the Army Reserve offers many other interesting opportunities. For instance, the Combat Casualty Care Course is one of the best trauma courses you'll find anywhere, civilian or military.

"The Army Reserve offers flexible scheduling for physicians. As part of my Reserve duty I might attend a civilian medical conference, teach, or do research.

"And I can choose short-term assignments in one of a variety of locations. I might have the opportunity to go abroad or work at any number of excellent medical centers such as Walter Reed."

If you would like more information about specific programs, such as the highly flexible augmentation program that Dr. Williams is in, call 1-800-USA-ARMY.

ARMY RESERVE MEDICINE. BE ALL YOU CAN BE.®

(Continued from Page 332)

IMMEDIATE OPENING. University affiliated ambulatory center. Full-time position available immediately in San Bernardino/Riverside, California. Competitive basic salary guarantee plus attractive fringe benefits. Contact Daniel Injo, MD, 22182 Barton Rd, Grand Terrace, CA 92324; (714) 370-1300.

SACRAMENTO, Internal Medicine or Family Practice. BC/BE with experience/training in Addiction Medicine. ASAM welcome. Kaiser Permanente has approximately 360,000 members in the Sacramento area. Active outpatient chemical dependency program. Hospital care for detox. No rehab. Dual diagnosis is handled by ourselves and psychiatry. At least 50 percent of time in addiction medicine with opportunity to evolve to full-time. Very attractive salary and full benefit package. Available in three months. Please contact David C. Meek, MD, Sub-chief, Alcohol and Drug Program, The Permanente Medical Group, Inc, 2025 Morse Ave, Sacramento, CA 95825; or call (916) 978-1495. EOE.

KAISER PERMANENTE

Good People Good Medicine

NORTHERN CALIFORNIA

Several positions available for Family Practice, Internal Medicine, and most medical subspecialties. We are a young, aggressive group in a well known prepaid group practice HMO organization with excellent benefits and a very reasonable call schedule. You will have a rewarding practice opportunity with ample time to enjoy the mountains and San Francisco which are nearby. If interested please call or send CV to Physician Recruitment, Administration, The Permanente Medical Group, Inc, 1305 Tommydon St, Stockton, CA 95210; (209) 476-3300.

OB DIRECTOR for a Family Practice residency program. Duties include teaching, performing cesarean sections and gynecological surgery. Some private patients. Salary of $120,000 a year plus malpractice insurance and bonus. Send CV to Ed Hughell, MD, Residency Director, 315 E. 13th St, Merced, CA 95340; or call (209) 385-7171.

VACANCY. GENERALIST at Las Vegas Medical Center. Staff physician to provide medical care of ICF and psychiatric patients. 40 hour week flextime, with extra pay for night and weekend call. Pleasant surroundings conducive to outdoor recreation. Excellent way to unwind after a life of strenuous private practice with rising insurance costs. Local university for any continuing education. Excellent fringe benefits. Contact Medical Director at (505) 454-2422, or Las Vegas Medical Center, Box 1388, Las Vegas, NV 87701.

FULL-TIME TRAVEL REQUIRED (one year minimum). Health research organization needs physicians for National Health and Nutrition Examination Survey sponsored by the US Public Health Service. Individuals will be part of a large medical team conducting health examinations in government examination centers traveling to 88 areas of the US through 1993. Physicians must be licensed in one state and specialized in Internal or Family Medicine. Competitive salaries, paid malpractice, per diem, car, four weeks paid vacation per year, holidays, and health, life, dental, disability insurance offered. Call Beverly Geline at (800) 937-8281, ext 8248. Westat, Inc, Rockville, Maryland. EOE/M/F/V/H.

KAISER PERMANENTE
Northwest Permanente PC
Physicians and Surgeons

OREGON/SOUTHWEST WASHINGTON

Excellent opportunities available for BC/BE Family Physicians in Oregon and southwest Washington. Openings available in the Portland/Vancouver area (full-time and half-time); Longview, Washington; and Salem, Oregon. Group provides a full range of professional services to 20,000 to 380,000 Kaiser Permanente members depending on location. Excellent salary/benefits; senior physician standing after two years; sabbatical; paid liability coverage.

Forward CV and inquiry to

Regional Medical Director
Northwest Permanente
3600 N. Interstate Ave
Portland, OR 97227.

UTILIZATION REVIEW POSITIONS

Cost Care, the nation's leading independent utilization management company, is seeking BC physicians to staff the medical services department. These part-time positions will include intensive training in all aspects of health care cost containment including pre-certification, home health care and case management. Prior Utilization Review experience is a plus, but not mandatory.

If you are seeking new skills in the changing health care marketplace, please submit your CV to:

Alan R. Greenfield, MD, MBA
Vice President
Medical Services
COST CARE, Inc
17011 Beach Blvd, Ste 400
Huntington Beach, CA 92647

WASHINGTON. BC/BE General Internists to join expanding 32 physician multispecialty group located in the foothills of the Blue Mountains. Excellent schools, cultural, and recreational opportunities. One junior college and two four-year colleges are located in the community. Guaranteed income with excellent benefit program. Send CV to Connie Goude, 55 W. Tietan, Walla Walla, WA 99362.

ARIZONA—GENERAL INTERNISTS. US trained, BC/BE to join busy growing private three MD practice. Excellent salary and benefits package. Reply to Number 191, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

SAN JOSE, CALIFORNIA. Urgent Care. Positions currently available for experienced physicians to provide primary care services at hospital based Urgent Care Center in San Jose. Minimum guarantee of $100,000 plus annual for 42 hour work week with one month vacation and paid malpractice. No night call. Please contact Nanette Peter at AEP, (408) 293-8881.

ORTHOPEDIC SURGEON. Orthopedic Surgeon for busy orthopedic service in 230-bed teaching hospital with residencies in General Surgery, Internal Medicine, OB/GYN, and Family Practice. Should be BC/BE. Experience in Arthroscopy preferred. Salary and compensation plan negotiable depending on experience. Hospital located in beautiful northern San Joaquin Valley close to major cities and skiing areas. Submit CV and references or contact Kenneth Young, MD, Chief of Orthopedics, San Joaquin General Hospital, PO Box 1020, Stockton, CA 95201; (209) 468-6611. AA/EOE.

CALIFORNIA. Fellowship in Ambulatory Pediatrics available January, 1990. Active clinical service in major medical teaching center with over 70,000 outpatient visits per year. Opportunity for clinical, teaching, administration, and research training. Contact Laura Wachsman, MD, LAC/USC Medical Center, Pediatric Pavilion, 1129 N. State St, Rm 1D37, Los Angeles, CA 90033; (213) 226-3624.

NORTHERN CALIFORNIA

Three residency-trained BC Family Practitioners seek a fourth who is a BE/BC to join them immediately in their community health center practice. Located on the eastern slopes of the Sierras in northeastern California. Practice entails a full scope of Family Practice including Obstetrics. Full hospital privileges. Excellent opportunity for recreation in local mountains including fishing, hiking, bicycling, camping, waterskiing, windsurfing, sailing, and in the winter both downhill and cross-country skiing. Includes a complete benefit package: malpractice coverage, health insurance, vacation, CME, etc. Salary commensurate with experience. Staff includes two family nurse practitioners, one physician assistant, family therapist, registered dietician, two health educators, and two prenatal instructors. Teaching opportunities available. If interested, send CV to **NRHC, Inc, 1306 Riverside Dr, Susanville, CA 96130, Attn: Paul W. Holmes, MD, Medical Director; or call (916) 257-5563.**

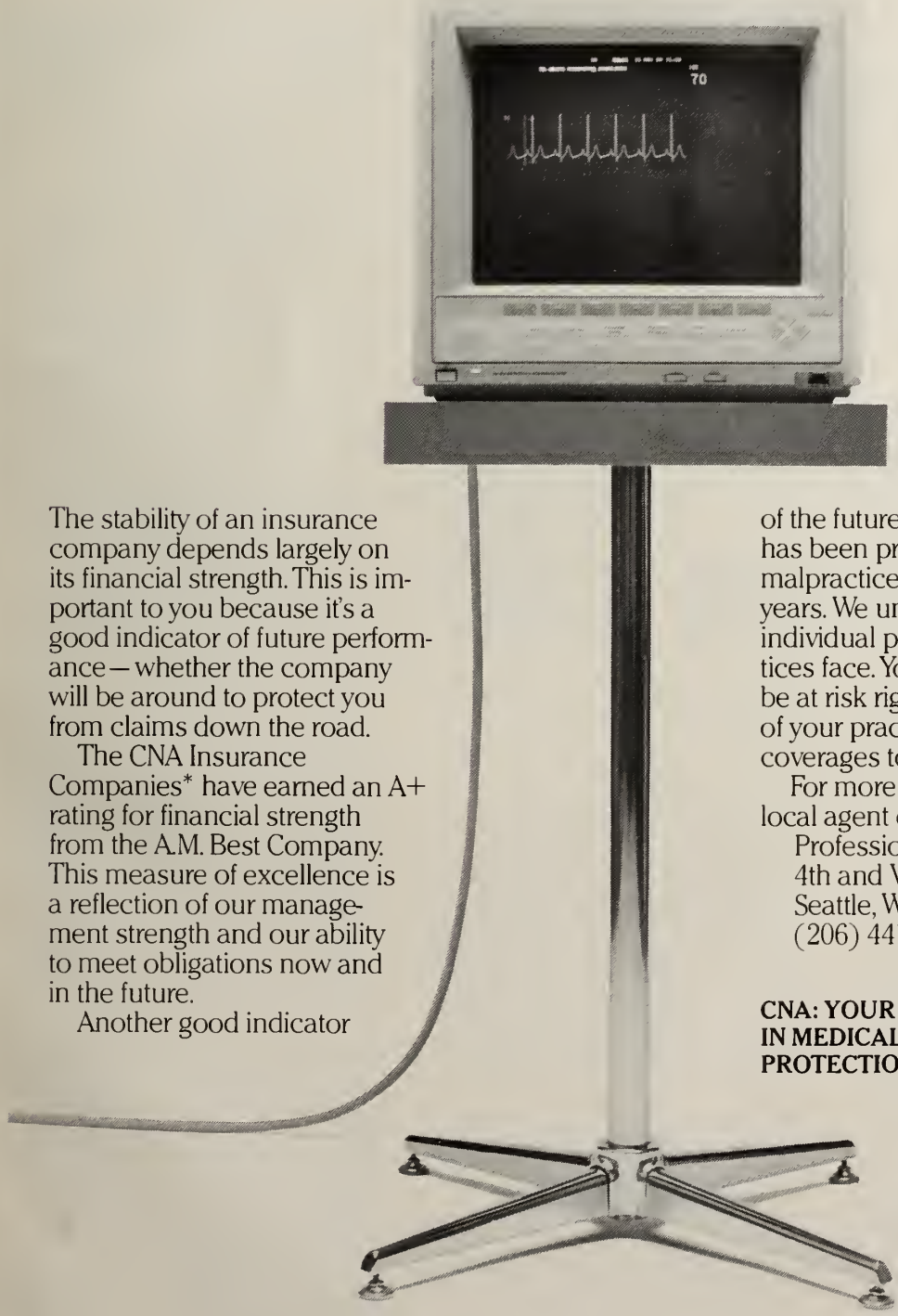
PRIMARY CARE PHYSICIAN. Rainier School, Washington state's largest residential care facility for the developmentally disabled adults is seeking an Internist or a physician. Excellent insurance and leave benefits. Salary negotiable up to $68K (Internist) or $62K (physician). Contact Dr Ruvalcaba, Clinical Director, Rainier School, PO Box 600, Buckley, WA 98321; or call (206) 829-1111, ext 494.

NORTHERN CALIFORNIA—SACRAMENTO. Leading HMO is seeking a BC/BE inpatient and outpatient Family Practitioner. Inpatient responsibility extends to physicians' individual practice only. Emphasis on Internal Medicine, Gynecology, and Orthopedics. No OB, limited Pediatrics. Must work outpatient clinic one night per week and one weekend day per month. We offer many benefits including malpractice insurance, medical, dental, and group life insurance, vacation, sick, and educational leave, excellent retirement benefits, and special arrangements for physicians transferring from established practice. For more information, please send CV to Dr J. Berger, Kaiser Permanente Medical Center, 6600 Bruceville Rd, Sacramento, CA 95823. EOE.

EXCEPTIONAL GROUP PRACTICE OPPORTUNITY for an Internist to join two other Internists. Located in southeastern Utah in the city of Price, near scenic national parks, great skiing, and other outdoor recreation. Excellent educational facilities including a junior college. Primary service area is approximately 30,000 people. Contact Tad Morley, Castleview Hospital, 300 N. Hospital Dr, Price, UT 84501; (801) 637-4800.

(Continued on Page 336)

CNA's financial stability can be vital to the health of your practice.



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(Continued from Page 334)

CALIFORNIA—NORTHERN. Area's leading private practice group has immediate and future positions for BC/BE Family Practice and Primary Care Physicians in its Department of Ambulatory Care and General Medicine. Excellent compensation, incentive program, full benefits, early equity position, retirement plan. Experience lifestyle and professional fulfillment in beautiful northern California. Call Maureen Forrester: (408) 282-7833. Send CV to San Jose Medical Group, Inc, 45 S. 17th St, San Jose, CA 95112.

PHOENIX AREA. Behavorial Health Program seeking additional adult psychiatrist. Center provides child through adult inpatient, outpatient and partial hospitalization, adult and adolescent CD. Fee-for-service with shared call, or association with existing staff are options. Hospital provides competitive financial support. For more information, call Greg Peterson, E. G. Todd Associates, at (800) 776-7330, or collect (913) 341-7806.

PRIVATE MEDICAL GROUP

seeks retina specialist for full-time office and surgical practice. BE, California license, training in retinal surgery, bilingual in English and Spanish. $65,000 per year. Send résumé to **San Diego Surgeons Medical Group, 480 Fourth Ave, Ste 307, Chula Vista, CA 92010.**

THE UNIVERSITY OF ARIZONA. Department of Internal Medicine, Section of Hematology/Oncology and The Arizona Cancer Center. Faculty Position. Director, Minorities Cancer Control Activities and Clinical Instructor, Internal Medicine. Applications are invited for a faculty position as clinical instructor in Internal Medicine (Medical Oncology) and administrative responsibility to develop cancer prevention and control research activities in the Hispanic community in Arizona. Experience in development of research grants would be of definite value.

Candidates for this position must be BE in Medical Oncology, have teaching experience in both prevention and treatment in clinical trials research, and a strong and proven commitment to teaching and academic medicine. Additionally, the candidate must be fluent in both Spanish and English as the position requires knowledge and understanding of the special needs of the Hispanic community and the ability to develop a program that can satisfy these needs. The candidate must have adequate experience in public health, knowledge, understanding, and ability to work with the Mexican Health System, and a strong commitment to developing clinical and prevention trials specific to the Hispanic community, as well as some experience in the development and funding of such trials. The successful candidate will be expected to have an excellent ability to work and communicate bilingually with patients at the Arizona Cancer Center and in the community. The position will be supported primarily by competitive research grants in cancer prevention and control awarded to the Cancer Center. The successful applicant will be housed in the newly completed Arizona Cancer Center facility at the University of Arizona. Salary: $40,000 per year.

Applicants should provide a CV, two copies of recent representative publications, and a detailed description of research goals as well as documentation of proficiency in the Spanish language and experience with Mexican health systems. The applicant should also arrange for three letters of recommendation to be sent directly to us. Applicants should respond by April 1, 1990. The University of Arizona is an Equal Opportunity/Affirmative Action Employer and applications from female and minority group members are strongly encouraged. Submit applications to Sydney E. Salmon, MD, Director, Arizona Cancer Center, Cancer Center Search Committee, Arizona Cancer Center, Rm 2912, The University of Arizona College of Medicine, Tucson, AZ 85724.

HAWAII. Family Practitioner needed for rural underserved area. Full-time position in nonprofit community health clinic. No OB, hospitalizations optional. Desire dedicated person to work in multicultural setting. Contact Alan Chun, MD, Waianae Coast Comprehensive Health Center, 86-260 Farrington Hwy, Waianae, HI 96792; (808) 696-7081.

BE/BC ORTHOPEDIC SURGEON

Contra Costa County Health Services is seeking an Orthopedic Surgeon to direct patient care and supervise teaching in a family practice residency/community hospital setting in northern California. Salary and benefits negotiable. For information, contact:

Frank J. Puglisi, Executive Director
Hospital and Clinics
(415) 370-5100

CALIFORNIA-CENTRAL COAST. Due to continued growth within our multispecialty medical group we have a need for a second OB/GYN specialist. Income based on productivity and commensurate with background/experience. Send CV to Mr Roger Bunch, Arbor Medical Group, 1414 E. Main St, Santa Maria, CA 93454; or call (805) 349-0508.

GENERAL INTERNIST. Multispecialty group located in San Luis Obispo, California, seeks a BC/BE physician. Fringe benefits plus practice costs paid and shareholder status. Submit your CV to Physicians Recruitment, San Luis Medical Clinic, 1235 Osos St, San Luis Obispo, CA 93401.

FAMILY PRACTITIONER. Multispecialty group located in San Luis Obispo, California, seeks a BC/BE physician. Fringe benefits plus practice costs paid and shareholder status. Submit your CV to Physicians Recruitment, San Luis Medical Clinic, 1235 Osos St, San Luis Obispo, CA 93401.

GASTROENTEROLOGIST. BC/BE to join two physician busy GI practice in Phoenix, Arizona. Must be trained in all endoscopic procedures. Excellent opportunity. Send CV to G & E, Ltd, 5040 N. 15th Ave, #308, Phoenix, AZ 85015.

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Currently seeking California and Nevada state licensed BC/BE physicians specializing in Orthopedic Surgery, Neurology, and Internal Medicine to perform Workers' Compensation and personal injury evaluation and treatment in our California and Nevada offices.

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Qualified candidates please send CV and references to:

Mr Donald Abramsky, MBA
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Facey Medical Group, Inc
11211 Sepulveda Blvd
Mission Hills, CA 91345-1196
(818) 365-9531

NORTHERN CALIFORNIA. The Permanente Medical Group, Inc, has immediate openings for BC/BE General Internists at the Roseville facility. Kaiser Permanente is a leader in health care, providing quality medical care to a rapidly growing population. We offer a tremendous benefit package and starting salary for career oriented physicians. Roseville is a foothill community located 90 miles from San Francisco and 100 miles from Lake Tahoe and Sierra skiing. University affiliation and teaching appointments are available. Send CV to Tony Cantelmi, MD, The Permanente Medical Group, Inc, 1001 Riverside Blvd, Roseville, CA 95678. EOE.

CALIFORNIA. Seeking BE/BC Pediatricians to staff busy inner city Pediatric emergency room in major teaching center with over 40,000 visits per year. Opportunities for flexible scheduling and various shifts. Full-time or part-time. Contact Dee Hodge III, MD, Dept of Pediatrics, LAC/USC Medical Center, 1129 N. State St, Rm 1D37, Los Angeles, CA 90033; (213) 226-3632.

AMBULATORY CARE. Full-time/part-time openings, northern, southern, and central locations. Competitive salary, strong incentive package, and growth potential. Malpractice paid. Join our partnership of established Emergency Medicine and Ambulatory Care Physicians. Contact Jane Dressler, California Emergency Physicians, 2101 Webster St, Ste 1050, Oakland, CA 94612-3027; (415) 835-7431 or (800) 842-2619.

GIG HARBOR, WASHINGTON—INTERNIST. Excellent opportunities in rapidly growing bedroom community for Tacoma and Seattle. Existing medical complex has 19 different health care professionals. Build to suit or finished space available. Information—Dr Jon H. Kvinsland, 5122 Olympic Dr NW, #A201, Gig Harbor, WA 98335; (206) 851-9171.

CALIFORNIA LICENSED BC RADIOLOGIST for back-up locum tenens, plus potential full-time. Contact I.V. Radiology Medical Group, 1266 Pepper Dr, El Centro, CA 92243; (619) 352-5666 after 6 pm.

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(Continued on Page 337)

(Continued from Page 336)

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If interested and qualified, please send C.V. and salary requirements to: **Employment Services, (PSW-22), EG&G Idaho, Inc., P.O. Box 1625, Idaho Falls, Idaho 83415.** We are an equal opportunity employer. M/F/H/V. **Minority candidates are encouraged to apply.** U.S. citizenship required.

EG&G Idaho, Inc.

NORTHERN AND SOUTHERN CALIFORNIA OPPORTUNITIES. We are retained by several hospitals and group practices as far north as the Oregon border, within one hour of San Francisco, Los Angeles, and major central valley cities including Bakersfield and Fresno, and as far south as San Bernardino. Our clients offer outstanding solo, group, hospital based, and HMO practices. Positions are salaried and/or fee-for-service. Typical offers include benefits, CME, and moving expenses. Current needs are for BC/BE Family Practice, Pediatrics, Internal Medicine (all subspecialties), Cardiology, OB/GYN, Orthopedic Surgery, ENT, Urology, and Neurology. Call or send CV to Ken Baker, The Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

INTERNAL MEDICINE OPPORTUNITY in beautiful resort region of central Oregon. Mountains and lakes surround this small community offering unlimited recreational amenities. World class skiing an hour from town. Strong and growing economy, good schools and low cost of living. Practice in either group or solo setting with full hospital and medical staff support. Competitive income package and excellent potential. Contact Bryan Bassett, Jackson and Coker, 115 Perimeter Center Pl, Ste 380 WJMO, Atlanta GA 30346; 1 (800) 544-1987 or 1 (800) 288-7030.

LIVE AMONG THE REDWOODS. Successful surgeon seeks partner for busy General and Vascular Surgery practice on northern California coastline. 85-bed hospital supportive of practice—will provide guarantee and malpractice. Call Gwyneth Anderson for more details about this ideal opportunity at (800) 221-4762, or collect (212) 599-6200. E. G. Todd Associates, 535 Fifth Ave, Ste 1100, New York, NY 10017.

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Rare opportunity for physician—BC in Occupational Medicine—to join **LARGE**, well established Industrial Medicine practice. Seeking dynamic, motivated individual possessing strong clinical skills. Ideal candidate would also enjoy interfacing with employers, insurance companies, and other members of the safety and health care team. Excellent income potential and benefits. Please reply to:

Carol Hewes, Director
1800 Westwind Dr, Ste 401
Bakersfield, CA 93301
(805) 324-8811

BC/BE INTERNIST NEEDED. Opportunity to join part of a comprehensive medical group practice located in the suburbs of San Francisco. Professional setting of 36 physicians. Forward CV to Peter Earley, Physician Relations, Ross Valley Medical Group, 2200 Larkspur Landing Circle, Ste 103, Larkspur, CA 94939.

OB/GYN. MD BE/BC NEEDED in northern California. Opportunity to join part of a comprehensive medical group practice. Professional setting of 36 physicians. Beautiful suburb of San Francisco. Forward CV to Peter Earley, Physician Relations, Ross Valley Medical Group, 2200 Larkspur Landing Circle, Ste 103, Larkspur, CA 94939.

INTERNISTS—SOUTHERN CALIFORNIA. Forensic Medical Company looking for MD who is bright, creative, and able to assimilate facts into medical reports. Primarily Workers' Compensation referrals. Part-time initially. Send CV to D. Salrin, 3600 Wilshire Blvd, Ste 1908, Los Angeles, CA 90010; (213) 384-8200.

SAN FRANCISCO BAY AREA multispecialty group seeks Pediatrician BC/BE, to join 26 congenial men and women delivering quality care in a combined fee-for-service, HMO/PPO setting. Bay Valley Medical Group, Attn: Daniel Rowe, MD, 27212 Calaroga Ave, Hayward, CA 94545; (415) 785-5000.

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(Continued on Page 338)

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FAMILY PRACTICE. San Diego East County. Gross over $300,000. Beautifully decorated and well equipped. Practice Consultants, (619) 528-2321.

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SOUTHERN CALIFORNIA General Practice for sale. High volume practice in fast growing area. Internal Medicine or General/Family Practice. Palm Springs weather, two hours from San Diego. Price and terms negotiable. Reply to Number 192, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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Alaska State Medical Association—2401 E 42nd Ave, Suite 104, Anchorage 99508. (907) 562-2662. Annual Meeting: June 7-9, 1990, Alaska Land, Fairbanks.

Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 7-9, 1990, Wyndham, Paradise Valley.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 3-8, 1991, Bally's Grand Hotel, Reno.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 13-16, 1990, Keystone.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 12-14, 1990, Ilikai, Honolulu.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 26-28, 1990, Sun Valley.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 4-6, 1990, Sheraton, Billings.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: June 21-23, 1990, Hyatt, Lake Tahoe.

New Mexico Medical Society—7770 Jefferson, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: May 4-5, 1990, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): April 27-29, 1990, Ashland.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 12-14, 1990, Marriott Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 19-22, Sheraton, Spokane.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 14-16, 1990, Jackson Lake Lodge, Moran.

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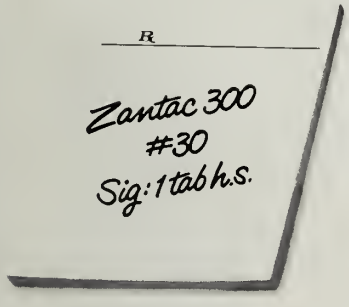
In active duodenal ulcers

Once-a-night h.s. therapy controls acid rain

Zantac® 300
ranitidine HCl/Glaxo 300 mg tablets



ZANTAC® 150 Tablets
(ranitidine hydrochloride)
ZANTAC® 300 Tablets
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in ZANTAC® product labeling.

INDICATIONS AND USAGE: ZANTAC® is indicated in:
1. Short-term treatment of **active duodenal ulcer**. Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer**. Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD)**. Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: General: 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.
2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION**). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions which suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, E coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: *Teratogenic Effects: Pregnancy Category B:* Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with oral ZANTAC®. The relationship to ZANTAC therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ZANTAC administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: Rare reports of tachycardia, bradycardia, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid IV for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Reversible blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. Rare cases of agranulocytosis or of pancytopenia, sometimes with marrow hypoplasia, have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ZANTAC® (ranitidine hydrochloride) and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg twice daily. An alternate dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ZANTAC® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day.

GERD: The current recommended adult oral dosage is 150 mg twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: ZANTAC® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) and unit dose packs of 100 tablets (NDC 0173-0393-47).

ZANTAC® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 tablets (NDC 0173-0344-42) and unit dose packs of 100 tablets (NDC 0173-0344-47).

Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

August 1987

Glaxo

Glaxo Inc.
Research Triangle Park, NC 27709

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ZAN325R

Printed in USA

October 1987

CONTROL ACID RAIN

with once-a-night h.s. therapy for active duodenal ulcers

Zantac® 300

ranitidine HCl/Glaxo 300 mg tablets

Glaxo ROCHE

See adjacent page for Brief Summary of Product Information